VOLUME VIII 1929

MEDICINE

Analytical Reviews
of
General Medicine
Neurology and Pediatrics

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THE TOXEMIAS OF PREGNANCY

H. J. STANDER

The Johns Hopkins University and Hospital

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THE TOXEMIAS OF PREGNANCY

INTRODUCTION

By the term "Toxemias of Pregnancy" is usually understood a group of disorders associated with gestation, which account for about 26 per cent of the total maternal mortality incident to child-birth. To correctly classify, determine the etiology of, and successfully treat these disorders, has been, and still is, one of the most important problems in obstetrics. Fortunately, the incidence of these disturbances is relatively small, and pregnancy follows an uneventful course in the majority of cases. Normal gestation is always accompanied by marked alterations in metabolism, and because the toxemias of pregnancy may be intimately associated with these metabolic changes, it is necessary that the latter be given due consideration before one discusses the toxemias of pregnancy.

CHANGES DURING NORMAL PREGNANCY

We are still in the dark as to the exact nature of the stimulus which gives rise to the very marked anatomical and physiological changes occurring in the mother during gestation. From the investigations of of Kruieger and Offergeld it is fairly well established that the central nervous system has no influence on pregnancy and the only effect the sympathetic system may have is on the maternal circulation. Goltz and Ewald have removed the entire lumbar cord in bitches without disturbing the progress or even the onset of pregnancy. It is, therefore, quite probable that stimuli of a chemical nature are responsible for the changes attending normal pregnancy. One immediately thinks of the corpus luteum. Ash-Upmark reports the completion of a normal pregnancy 269 days after bilateral oöphorectomy had been performed. He furthermore collected several cases from the literature where complete castration had been effected during the first month of gestation without interruption of the pregnancy. We are as yet unable to state whether or not any hormone or hormones arising

from the corpus luteum or ovary are essential to the onset of pregnancy, although we are certain that in the human, at least, pregnancy may proceed from the first few weeks to a successful completion without the aid that may come from the ovary.

It is conceivable that the stimulus for the maternal changes may come from the foetus or from the placenta. Starling suggested that such a stimulating hormone may be in the tissues of the foetus. Halban believes that a placental hormone is responsible for the enlargement of the mammary gland. Cova has made extended experimental studies of placental secretions and states that alcoholic extracts of the placenta will produce hypertrophy of the uterus, vagina and mammae, and that such endocrine glands as the ovaries, adrenals and thyroid will undergo greater development as a result of the action of the internal secretion of the placenta. Guggisberg also regards the placenta as an organ of internal secretion. Abderhalden thinks there are specific ferments depending upon the placenta.

The exact nature of this stimulus has not yet been determined, although the weight of the evidence indicates that it is a chemical substance, probably a hormone, arising in the placenta or foetal tissues, which is responsible for the anatomical and physiological changes in the maternal organism.

1. Weight

As early as 1862, Gassner showed that there was a progressive increase in the weight of the mother greater than the increase in the weight of the foetus and the reproductive organs. This is undoubtedly due to an increase in other parts of the mother's body. Davis, who studied 150 cases, found that the average gain during pregnancy was 21 pounds and the average weight of babies, 6 pounds and 15 ounces. Zangemeister showed that the pregnant woman reaches her greatest weight the third day before the onset of labor, and that in the few days immediately preceding labor, there is a definite loss in weight. His results were in part corroborated by Hirsch who found that the greatest weight was reached on the sixth day before labor, and that from the sixth to the fourth day preceding labor, the weight remained stationary. He also observed a decrease in weight immediately preceding labor. Hirsch regards the hypophysis, which becomes active

at the beginning of labor, as responsible for this decrease in weight. Kemper on the other hand thinks that the loss of weight preceding labor and amounting to about 1 kgm. can be explained by an increase in excretory function of the mother as well as by a lessened food intake. Hannah believes that the gain in weight in the mother is greater in the primipara than in multipara.

Zangemeister has for a long time claimed that the loss of weight at the end of pregnancy is a sign of impending labor. Biehle, who has made a careful study of 40 selected healthy pregnant women, without any signs of toxemia, found such a decrease in weight in only 63 per cent of his cases, and does not agree with Zangemeister that the weight of the patient at the end of pregnancy is an index as to whether or not pregnancy should be terminated.

We may conclude that the maternal organism undergoes a progressive increase in weight, until shortly before labor, that this increase in weight is far greater than the increase in weight accounted for by the product of conception and the growing uterus with its adnexa, and that immediately before labor there is a reduction in the weight of the mother, amounting to about 1 kgm., but that this reduction in weight is not always a satisfactory index of impending labor.

2. Blood volume

It is the general opinion that the maternal blood volume increases steadily during pregnancy. Kaboth has estimated that the total increase in blood volume during gestation is about 400 cc. Gueissaz and Wanner, by injecting glucose and noting the refractive index of the serum, observed an increase in blood volume amounting to approximately 15 per cent. Miller, Keith, and Rowntree, using the vital red method, as well as Stander and Creadick, working with the carbon monoxide method on dogs, noted an increase in the maternal blood volume. Bohnen and Borrman by injecting congo-red intravenously found the average normal in healthy non-pregnant women to be 6.4 per cent, in the first half of pregnancy 7.63 per cent and at the tenth month 7.0 per cent. The dye methods measure the plasma, the carbon monoxide or cell method measures hemoglobin, consequently the total blood volume must be the sum of these two. Also the ratio of

plasma to cells is not constant; yet, bearing in mind these considerations the experimental work to date indicates that in the latter half of pregnancy there is a definite increase in blood volume.

While considering the blood volume it is advisable to know the behavior of the blood moisture. Pregnancy seems to be associated with a dilution of the blood. The specific gravity of the blood was investigated by Nasse, Lloyd-Jones, and Zangemeister, and these authors are agreed that a decrease in specific gravity takes place as pregnancy proceeds. From these observations as well as from the work on the distribution of serum proteins by Plass and others, it is fairly certain that pregnancy brings about an increased hydration of the blood. Stander and Tyler state that during gestation the water content of the blood is usually between 77 and 82 per cent, the accepted normal limits. Furthermore, when the blood moisture is determined month by month during pregnancy, characteristic fluctuations become apparent. It increases gradually, until the seventh month, and subsequently remains stationary, or slowly decreases. At the onset of labor it is approximately the same as at the beginning of pregnancy, and the act of labor has no constant influence upon the blood moisture. Plasma presents the same type of variation as that shown by the whole blood. Schmidt, Bickenbach and Jonen experimenting on dogs found the blood water content to increase during pregnancy. Gestation is undoubtedly accompanied by an hydration of the blood and a true increase in blood volume, which is perhaps associated with a decrease in red cell count and hemoglobin percentage.

3. Protein metabolism

There are many investigations on protein metabolism during pregnancy. The pregnant woman undoubtedly absorbs protein as well as the non-pregnant, as shown by the observations of Hoffström in a primipara during the last months of pregnancy. Pregnancy represents a gain in nitrogen in the mother.

Experiments of Hoffström showed that there was a very definite positive nitrogen balance during the second half of pregnancy. He carefully studied the nitrogen intake and output from the sixteenth week until the end of pregnancy, and found that the mother completed

the pregnancy with a net gain of 209 grams of nitrogen. Wilson followed the nitrogen balance in three normal pregnancies, and came to the conclusion that in normal pregnant women, a storage of nitrogen begins at a very early period, and that the amount of nitrogen stored is greatly in excess of the actual needs of the developing ovum. It is fairly well established from the work of these investigators, as well as of Mahnert, Bar, and Landsberg that there is a positive nitrogen balance during pregnancy and particularly during its second half.

Eufinger examined the various protein fractions of the blood during pregnancy and found that they underwent a change or shifting. His findings show a relative decrease in total proteins, and a progressive increase in fibrinogen, globulin and euglobulin, but a marked decrease in albumin; and in 350 women during pregnancy there was a marked decrease in the stability of the plasma colloids, as tested by the Gerloczy reaction.

Plass and his co-workers have also made a study of the different protein fractions in the blood plasma of normal pregnant women. These investigators found that beginning with the third month of gestation, there is a gradual diminution of plasma protein, and that this decrease reaches its maximum at the fifth month. During the last few months of pregnancy, the dilution tends to be less marked, and there is a further concentration at the time of labor. They further observed that the relative plasma volume as measured by hematocrit readings, follows inversely the plasma protein concentration, and therefore, they regard the decrease of the plasma protein as a result of true dilution. Plass concludes that the plasma proteins tend to decrease during pregnancy and the early part of the puerperium; that the serum albumin is decreased to such an extent that the drop in the total proteins can be explained by the concentration of this fraction; and that fibrinogen increases during pregnancy while the serum globulin shows only a slight relative increase, the absolute values remaining constant. Kraul also demonstrated that the fibrinogen content of the blood increases during pregnancy, rises still more during labor, and slowly returns to its normal level during the puerperium. This author believes that increased fibrinogen plays some part in the production of thrombosis following delivery. This increase in fibrinogen in the human being during gestation is further proven by the work of Muller and Dienst. Schmidt,

Bickenbach and Jonen investigated the fibrinogen content of the blood in dogs, and found that pregnancy was associated with a very definite increase of fibrinogen content of both whole blood and plasma.

At present there is some controversy concerning the amino acids of the blood during pregnancy. The amino acids are composed of very definite fractions, which, according to Hellmuth, may be grouped as (1) alphatic mono-amino-acids (glycocoll); (2) alphatic di-amino-acids (lysin, arginin); (3) aromatic and heterocyclic amino-acids with and without primary amino-N (histidin and prolin). Hellmuth is of the opinion that there is no marked change in any of these during pregnancy. Schlossman is also convinced that pregnancy is not associated with a change in amino-acid content of the blood. Runge and Juhl found that in normal pregnancy there was 32 mgm. per cent of amino acid in the blood, as compared with 27.3 mgm. in normal non-pregnant women. Frey, on the other hand, found a very marked increase in amino acids during pregnancy. From a careful study of all the results reported in the literature it seems safe to conclude that there is no marked change in the amino acids during gestation.

We have seen what profound alterations in protein metabolism accompany gestation and it is thus reasonable to expect differences in the excretion of nitrogen in the maternal organism. As early as 1894 Zachrjewski showed a decreased excretion of nitrogen in the urine during pregnancy. According to the investigations of Hasselbach, the woman in the latter half of pregnancy excretes 9.2 grams nitrogen every day, whereas immediately after birth her daily output of nitrogen rises to 11.4 mgm. Mahnert, in an attempt to determine whether or not the increase in weight during pregnancy is due to a sparing of nitrogen, studied the total metabolism in pregnant women from the fourth to the tenth month. He came to the conclusion that there was a definite increase in the protein metabolism, and is of the opinion that the increase in body weight can be explained on this basis. He furthermore believes that the terminal loss in weight, discussed above, is due to an increase in protein metabolism, although he was unable to determine the cause or causes of such an increase in protein metabolism immediately preceding labor.

Bock finds that the C:N ratio is increased during pregnancy (*C* is the elementary organic carbon, and *N* the nitrogen, in the urine).

This C:N ratio in the urine is supposed to be an index of the degree of oxidation of intermediary metabolism products. An increased excretion of *C* denotes a decrease in the oxidative processes of the intermediate metabolism. Bock concludes that in normal non-pregnant persons the ratio C:N is 0.85 (Bickel); that in pregnancy this ratio increases to 1.13; and that this increase in C:N ratio is due to an increase in carbon as well as to a decrease in the nitrogen excretion.

Murlin studied the distribution of the nitrogen fractions of the urine in three cases of normal pregnancy. Both Bar and Murlin showed that there is a diminished excretion of urea in the urine during pregnancy and an alteration in the nitrogen distribution in the urine, because while the amount of urea excreted is diminished the quantity of ammonia or the so-called "ammonia coefficient" is increased. Wilson showed that the amino acid nitrogen in the urine is increased, and Falk and Husky have demonstrated polypeptide nitrogen in the urine of pregnant women. It is of interest to note that creatine appears in the urine during the latter part of pregnancy, as first shown by Krause and Cramer and amply confirmed by later investigations.

After having studied the positive nitrogen balance during the latter half of gestation, the changes in the protein fractions of the blood and the altered nitrogen partition in the urine accompanying pregnancy, it is essential that we inquire into the non-coagulable or non-protein nitrogen of the blood. As the result of the findings of a large number of workers (Folin, de Wesselow, Williams, Hellmuth, Plass, Stander, King and Denis, Harding, Allin and Van Wyck, Bunker and Mundell, and Jung), we are able to state that the non-protein nitrogen content of the blood during pregnancy is the same as, or very slightly less than, in the normal non-pregnant woman, in the neighborhood of 30 mgm. per 100 cc. blood. Caldwell and Lyle found a slightly higher value in a series of 150 analyses on pregnant women.

In the normal non-pregnant woman the blood urea nitrogen forms approximately 50 per cent of the total non-protein nitrogen. Killian and Sherwin, Caldwell and Lyle, Williams, De Wesselow, Folin and Stander have found a lowering of this ratio during pregnancy. Dilution of the blood, decreased production of urea and an increase in the undetermined or rest-nitrogen are among the theories which may explain this lowering of urea-nitrogen to non-protein nitrogen ratio in the blood of the maternal organism.

Normal pregnancy is not associated with any marked changes in creatinine, creatine or uric acid in the blood, although it must be admitted that our method for determining creatine is still open to criticism.

4. Fat metabolism

Normal pregnancy is associated with a marked alteration in the concentration of the blood lipoids. During the latter part of pregnancy, fat, lecithin and cholesterol show a marked increase. Slemons and Stander found that at term there are approximately 900 mgm. of fat per 100 cc. of maternal blood, while the blood of the normal non-pregnant woman contains about 600 cc. of fat per 100 cc. These authors regard the increase in fat, lecithin, and cholesterol as a preliminary step in the preparation for lactation. Tyler and Underhill have corroborated these findings and conclude that the total neutral fat of whole blood in pregnant women becomes higher than the non-pregnant values as early as the third month of pregnancy, and that there is a progressive increase from then till term. They also found that cholesterol, cholesterol-esters and lecithin increase gradually until term, when each is roughly one-third higher than at the third month. Hellmuth, Hermann, Neumann and Lindemann and Chauffard-Grigaut come to the same conclusion, namely, that there is an increase in neutral fat as well as in lipoids during pregnancy.

5. Carbohydrate metabolism

It is well known that pregnancy is often accompanied by a glycosuria, although the amount of glucose in the blood may not be increased. The work of Kämpf, Bergsma, Benthin, Morris, Stander and Radelet, Hellmuth, and Novak and Bermann shows that the blood sugar during pregnancy is not elevated, and some of these authors even found values slightly below normal. The so-called pregnancy glycosuria is probably due to a lowering of the renal threshold for glucose (Nürnberger, Gottschalk), or it may be connected with excessive activity of the pituitary gland, as suggested by Wallis and Bose. After Schirokauer had examined the blood sugar in cases of pregnancy glycosuria, Grunthal experimented on many such patients and stated that the sugar tolerance figure in pregnancy is the same as in the normal

pregnant woman. This author came to the conclusion that the pregnancy glycosuria does not depend on the sugar level in the blood. During labor and often shortly before labor the sugar in the blood increases according to Walthard. Many pregnant women when subjected to a blood sugar tolerance test show glycosuria and this fact has been utilized by Frank and Nothmann to furnish a test for the existence of pregnancy. Bokelmann and Rother have given an excellent review of this subject and have also themselves tried the sugar tolerance test for pregnancy in 48 women. They came to the conclusion that the test is not of great value and that more reliance could be placed upon a clinical examination of the patient.

In considering the carbohydrate metabolism it is well that we bear in mind its relation with fat metabolism. It seems fairly well established that the usual relationship of carbohydrate to fat is disturbed during pregnancy. Acetone bodies (di-acetic and B-oxybutyric acids) are regarded as the intermediate oxidation products of the fatty acids, and their excretion in the urine is greatly increased when carbohydrates are witheld from the diet. Vicarelli in 1893 noted the presence of acetone bodies in the urine of pregnant women. A diet poor in carbohydrates (Porges and Novak, Harding) leads to an excretion of acetone bodies in the urine in a normal pregnant woman, while a non-pregnant woman on an identical diet will show no acetone in her urine. Bokelmann and Bock observed 39.48 mgm. acetone bodies per 100 cc. blood in normal pregnancy as compared with 29.85 in the non-pregnant woman. This increase in acetones in the blood they believe to be due to a deficient supply of carbohydrates, to an abnormal metabolism of carbohydrates or to a primary change in fat metabolism.

In addition to this increase of acetone bodies in the blood and the tendency towards acetonuria associated with pregnancy, there is also an increase in blood lactic acid, according to Bokelmann and Schultze. Lactic acid arises from carbohydrate and is formed during the contractile phase of muscular contraction. Most of the lactic acid formed is resynthesized to glycogen. Bokelmann believes that the lactic acid increase in pregnancy is a result of a slowing down in carbohydrate metabolism, a disturbance in oxidation of lactic acid to carbonic acid and water, or a retardation in the resynthesis of lactic acid to glycogen. Kielin, Zweifel, and Stander and Radelet were

unable to notice any marked changes in blood lactic acid during normal gestation.

6. Acid-base equilibrium

The alveolar CO_2 tension is lowered during pregnancy as first shown by Hasselbalch. This lowering of the CO_2 tension probably manifests itself as early as the second month of gestation according to very painstaking work of Hasselbalch and Gammeltoft. These investigators found the alveolar CO_2 tension during the latter stages of pregnancy to be from 30 to 35 mm. Hg, limits agreeing well with the observations of Rowe. The CO_2 combining power of the blood is also definitely decreased. Losee and Van Slyke, Cook and Osman, Slemons, Emge, Stander, Williamson, Bokelmann, Schmidt and Wingen, and others have noted a marked drop in the CO_2-combining power of the blood as pregnancy approaches term. Some authors believe this so-called "acidosis of pregnancy" to be dependent on the acetone bodies and lactic acid in the blood, as referred to above. As we shall see later, pregnancy means a great carbohydrate drain for the mother and Schmidt and Wingen believe that this increased carbohydrate requirement in pregnancy is met partly by fat being converted in the liver into glycogen, and that during this transformation acid by-products may appear and these use up some of the alkali reserve of the blood. This lowers the capacity of the blood for combining with CO_2, resulting in a lowered alveolar CO_2 tension.

This acidosis of pregnancy is probably a compensated one. Hasselbalch and Gammeltoft examined the hydrogen-ion concentration of the serum and found it to be slightly changed at the end of pregnancy. Bock gives the pH for normal people as 7.52, in the early months of gestation as 7.51 and at the end of pregnancy 7.47. After labor the pH returns to its normal value of 7.52. This author concludes that it is only during the last weeks of pregnancy that the actual reaction of the blood is changed, and that this slight change is brought about by the buffer capacity of the blood. We may conclude that pregnancy is associated with a relative acidosis, but that any change in the acutal reaction of the blood must be very slight.

7. Basal metabolism

There is little doubt that pregnancy is associated with an increase of the total metabolism of the mother. Magnus-Levy noted that the oxygen absorption in the eighth month of pregnancy was 17 per cent higher than at the third month. In the normal woman at term the basal metabolic rate is about 4 per cent higher than in the normal non-pregnant woman in complete sexual rest (Zuntz, Hasselbalch, Carpenter and Murlin). These authors found that the heat production per unit of weight for the puerperal woman was 11 per cent higher than for the normal non-pregnant, and 7 per cent higher than for the same woman at term.

In 1921 Baer reported the basal metabolic rate in 44 normal pregnancies. He observed that during the latter part of pregnancy, this rate averaged more than 30 per cent above the normal non-pregnant woman. Two years later Cornell investigated the basal metabolism in 84 pregnant women. He also found an increase in the basal rate. This increase in basal metabolism during pregnancy has been confirmed by Sandiford-Wheeler, Root-Root, Rowe, Alcott, Waldemier, and Stander and Peckham. The increased basal rate is probably dependent upon the growing product of conception, as well as upon an increased activity of the thyroid gland. Pregnancy probably does not result in any marked alterations in the energy exchange, beyond that produced by the growth of the foetus.

8. Mineral exchange

According to the work of Camerer and Soldner on the ash of the human foetus, there is a preponderance of calcium and phosphorus in the foetus, and these two substances are present in higher concentration in the foetal than in the maternal blood according to v. Oettinger. There must be a considerable drain on the mother as far as these two elements are concerned. According to the last author there is 10.2 mgm. per cent of calcium in the normal non-pregnant woman, whereas the figure for normal pregnancy is 9.8 per cent. His figures for inorganic phosphorus are 3.6 mgm. for non-pregnant individuals, and 3.3 for normal pregnancy. A slight decrease in calcium in the maternal blood has also been noted by Bock, Plass and Bogert, Ivanyi,

Rodecurt, Linzenmeier, Dibobes, Kvater, Schonig, Krebs and Briggs, Hetenyi, Liebmann, and Stander, Duncan and Sisson. A few authors (Serdjukoff, Morosova and others) observed no change in the calcium content of the blood during pregnancy, but the weight of evidence points to a slight lowering of the blood calcium, as the woman approaches term. The inorganic phosphorus is probably not much altered during gestation. De Wesselow and v. Oettinger noted a slight decrease, while Rodecurt observed a slight increase, and Bock and Stander could find no difference between the non-pregnant and pregnant values for inorganic phosphorus.

There is very slight difference in sodium in the pregnant and non-pregnant, v. Oettinger giving an average figure of 329.4 mgm. per cent for the non-pregnant woman. Harding, in his review on the metabolism of pregnancy, collected figures from various authors and believes that these show that sodium decreases slightly in concentration in the serum while there is an increase in the corpuscles, and that this also holds true for calcium and chlorine. Stander and his co-workers could find no marked change in sodium during pregnancy. The values for potassium and magnesium are also about the same for pregnant as for non-pregnant women.

The foetus must derive its iron from the maternal organism, and it gets a large part from the mother's hemoglobin. The foetus requires iron for building its own hemoglobin and for its nucleo-proteins. In the adult, nucleo-protein is probably the best source for iron required in the manufacture of hemoglobin, and it is possible that the foetus may get part of its iron from a food nucleo-protein or an organized nucleo-protein in the mother's blood. Williams feels convinced that the foetus takes up iron directly by means of the syncytium from degenerated maternal red blood cells. Charrin believes that the reserve iron of the mother is stored in the spleen and is reduced during gestation. It is interesting to know that much more iron is stored in the liver of the young rabbit at birth, than in an adult rabbit. This is probably true for the human foetus as well.

9. Hormones

The thyroid gland undoubtedly undergoes a change during pregnancy, becoming more vascular and showing a definite hypertrophy.

Davis, in a study of 520 women, found visible signs of thyroid hypertrophy in 41 per cent during early pregnancy. The enlargement is a true hyperplasia. The significance of hypertrophy of the thyroid gland is not yet clear. Halsted found that in pregnant dogs from which the thyroid gland was removed, the puppies showed a tremendous enlargement of the thyroid, indicating that there was a compensatory hypertrophy because of the lacking secretion in the mother. Seitz states that there is also an increase in colloids of the thyroid. The para-thyroid gland likewise undergoes a marked change during pregnancy. The chromophile cells multiply in number and are better outlined, from which one may deduce that their function is increased during pregnancy. We know that the para-thyroids are intimately associated with calcium metabolism and it is possible that the changes noted above in calcium are dependent upon the changes in the para-thyroid. We are unable to say whether the pancreas undergoes any morphological changes during gestation; although there is very little doubt that the carbohydrate metabolism is altered. The ovaries present differences during pregnancy. The corpus luteum of pregnancy is a well known entity, but, as stated earlier in this paper, pregnancy can proceed to a successful completion, even after the removal of both ovaries as early as the first month of pregnancy. On the other hand, the most characteristic change in the ovaries of pregnant women consists in atresia of the follicles, which is characterized by development up to certain stage without rupture, but with such hyperplasia of the connective tissue cells of the inner layer of the theca, as to suggest that they must have some internal secretory activity. These changes are so pronounced that any one familiar with the histology of the ovaries can readily differentiate between those derived from pregnant and those from non-pregnant women. There is little doubt that the adrenals present a marked hypertrophy of the cortex during gestation. Whether this means an increase in adrenalin in the body is not known. Some authors have tried to link up the change in carbohydrate metabolism with increased production of adrenalin. In 1904 Lauñois and Mulin showed that pregnancy was always associated with a hypertrophy of the hypophysis. It is the anterior lobe of this gland which undergoes regular hypertrophy, but the significance of this is far from clear. The posterior lobe of the gland does not

hypertrophy, although it is well established that it is this part of the pituitary which is connected with the stimulating effect on the uterine contractions. The placenta is regarded by many as an important organ of internal secretion. De Lee states that placental hormones stimulate the development of the uterus and probably activate the thyroid, para-thyroid, pituitary and adrenal gland. Some writers are of the opinion that the placenta when fully developed takes over the functions of the ovary and corpus luteum.

10. Neuro-vascular system

According to Freund 50 per cent of all pregnant women show dermatographism, and according to Hinselmann and Nevermann and others, 60 per cent of all pregnant women show capillary spasm. It would therefore appear that pregnancy is associated with changes in the sympathetic, and para-sympathetic systems. There are also certain blood diseases peculiar to pregnancy. Chlorosis, which was formerly so common among young girls, is said by some authors to develop during pregnancy. The total number of blood cells is decreased, although during the latter part of pregnancy there is a definite increase in the blood corpuscles. We are also acquainted with a pregnancy anemia which simulates pernicious anemia, but instead of terminating fatally it often eventuates in spontaneous recovery after the completion of the puerperium. This is supposed to be due to the destructive action exerted upon the maternal red cells by the chorionic epithelium. Pregnancy hemolysis, pregnancy hemoglobinemia and pregnancy hemoglobinuria also occur. Most authors believe this hemorrhagic diathesis to be due probably to a change in the endothelial covering of the capillary vessels. The white blood cells usually show a leucocytosis during normal gestation. The skin is often affected by gravidity. The pigmentation of the nipples and areola is is very common. Cloasma, or pigmentation of the face, occurs less frequently.

11. Heart output

As early as 1827 Larcher stated that pregnancy was always accompanied by a marked cardiac hypertrophy. Dreysel found that the heart of a pregnant woman invariably weighed more than that of a

normal non-pregnant individual. It has often been stated that true hypertrophy of the heart occurring during pregnancy, is caused by the placental circulation, compression of the aorta by the uterus, or by the increased circulation in and around the uterus. It has also been suggested that an increase in the output of the heart is caused by the increased peripheral resistance brought about by some vaso-constrictor substance circulating in the blood stream. Lockhead and Cramer examined extract of the placenta, and found that this contained no vaso-constrictor substance. There is no, or only a slight, increase in the blood pressure during normal pregnancy. Slemons and Goldsborough however, demonstrated a considerable increase in pulse pressure which was especially marked during the later months of pregnancy. Jaschke came to similar conclusions. The "cardiac output" measured directly in the dog, by Stander, Duncan and Sisson, revealed that during pregnancy the minute volume is markedly increased, being one-third to one-half greater than in the non-pregnant animal. Whether this increased output is the result of hypertrophy of the heart or not, has not yet been determined, but it seems probable that it is at least in part accomplished by drawing upon the reserve force of the heart. Frey, however, is convinced that actual cardiac hypertrophy does occur during normal gestation.

CLASSIFICATION OF THE TOXEMIAS OF PREGNANCY

We have seen what profound anatomic and metabolic changes take place in the maternal organism during normal gestation. Many of these alterations become more marked in the presence of a toxemia, and it has been the object of numerous clinical and experimental investigations by a vast number of workers to determine whether and, if so, in what manner, these various departures from the normal may be specifically linked up with the etiology and course of the different toxemic disorders. There has been one universal drawback in all this work, which is particularly evident when one attempts to correlate the ultimate findings of different investigators. This drawback has been, and still is, the lack of a uniform method of classifying the various types of toxemia of pregnancy. Different clinics are wont to use different classifications, a practice which has only served to confuse those who attempt to compare the work and results of these

different clinics. It is, of course, apparent that the real cause of such discordance is our profound ignorance concerning the etiology of the disorders which we are endeavoring to classify and study. As Kellogg of Boston very aptly puts it, "The conquest of the toxemia of pregnancy depends primarily on a universal acceptance in this country of some index, of some classification, some coöperative mode of study in every great obstetric center," and he very wisely suggests that a committee of representatives of the obstetrical societies meet with a view to establishing a working index or classification, tentative at first and changeable at each yearly meeting.

The main difficulty arises when an attempt is made to classify the so-called "pre-eclamptic" and "nephritic" toxemias which may complicate pregnancy. Vomiting of pregnancy, acute yellow atrophy of the liver, and eclampsia are well defined entities and usually recognizable. All agree that nephritis may complicate pregnancy, but it is sometimes rather difficult to recognize and classify the various types of kidney lesions during pregnancy and to make a differential diagnosis between the nephritic and pre-eclamptic toxemias. Indeed, it is often impossible to know with which condition we are dealing until the patient has reached the end of the puerperium, or has come to autopsy.

Williams in the last edition of his text-book classified the toxemias of pregnancy as follows: (*a*) pernicious vomiting (*b*) acute yellow atrophy of the liver (*c*) nephritic toxemia (*e*) eclampsia and (*f*) presumable toxemias. DeLee groups them as follows: hyperemesis, ptyalism, gingivitis, eclampsia and allied conditions, kidney of pregnancy and acute yellow atrophy of the liver. Under eclampsia and allied conditions he discusses eclampsia, eclampsia reflectorica, acute toxemia (eclampsia without convulsions) and nephritic eclampsia. Zangemeister in his recent book gives the following classification:— hyperemesis, hydrops, nephropathia and eclampsia. In the present discussion, the author is not considering such complications as chorea, skin affections, anemia, hemophilia, neuritis or psychoses.

There is a mild type of toxemia manifesting itself usually in the eighth or ninth month of pregnancy, and consisting of a slight elevation of blood pressure, a slight amount of albumin in the urine and moderate swelling of the ankles. As soon as the patient has been delivered the symptoms disappear completely, and in a subsequent pregnancy

the condition may recur or may be absent. Kellogg speaks of this as recurrent toxemia of pregnancy, and states that such a recurrence should be considered as a chronic entity distinct from the common kidney disease complicating pregnancy. Moreover, he is of the opinion that it may be subdivided into two groups: (1) in which under the strictest possible prenatal care the prognosis for both mother and child is good and (2) in which the prognosis for the child is bad, no matter what the prenatal care may be. Von Geldern studied the subsequent history of 27 women with toxemia of pregnancy, and found that 13 of them had one or more normal pregnancies following the toxemia; while 14 had a recurrence. He states that in cases of "recurrent toxemia" without permanent damage to the kidney, the prognosis is difficult. Stander and Peckham (1926) made a study of the toxemias in repeated pregnancies in the same individual and came to the conclusion that there is a group, which they designate as low reserve kidney, in which it is impossible to demonstrate any signs, symptoms or laboratory findings suggesting nephritis. It seems to the author that many of the "recurrent toxemias" belong in this category, as well as the simple "albuminuria of pregnancy."

Mussey has attempted to group the nephropathies of pregnancy, and has directed our attention to the classification of Volhard and Fahr, which is as follows:

A. Pyelitis and pyelonephritis.
B. Hypertension and nephritis.
    1. Acute nephritis
        a. Acute glomerulonephritis.
        b. Acute nephrosis.
    2. Chronic nephritis.
        a. Chronic diffuse glomerulonephritis.
        b. Chronic nephrosis.
    3. Sclerosis (vascular lesion)
        a. Benign hypertension.
        b. Malignant hypertension.

Mussey and Keith believe that the classification of nephritis during pregnancy into acute and chronic aids in establishing the prognosis. Patients with acute nephritis very rarely give a history of previous

kidney trouble. They state that in the acute type of nephritis, the presence of albumin in the urine, and the sudden rise in blood pressure with increased oedema, usually occur during the 8th or 9th month of gravidity, and that a kidney function test shows satisfactory excretion, with a urine of high specific gravity. On the other hand, patients with chronic nephritis often give a history of previous kidney trouble, and the hypertension, oedema and albuminuria make their appearance early in pregnancy, usually before the seventh month. In the latter, tests for renal function show poor excretion, with the specific gravity of the urine either fixed or low. These authors believe that it is possible to differentiate between the various types of nephritis during pregnancy. The subdivision of parachymatous nephritis into acute glomerulonephritis and acute nephrosis is of quite recent origin. In acute glomerulonephritis there is albuminuria, oedema, hypertension and hematuria, the urine output is lowered and there may be eye ground changes. In acute nephrosis, on the other hand, the blood pressure is essentially normal, there is marked oedema, albuminuria and lowered output of urine, but no nitrogenous retention in the blood nor any eye changes.

Mussey divides the toxemias of the later months of pregnancy into three groups: (1) acute toxemias of the eclamptic type; (2) toxemias due to exacerbations of chronic nephritis; and (3) toxemias due to definite renal infection (focal nephritis and pyelonephritis). He further subdivides the acute toxemias of the eclamptic type into (a) those in which there is unquestionably pathologic evidence of disease of the liver and (b) those in which the symptoms of renal involvement predominate.

Von Jaschke regards the "kidney of pregnancy," first described by Leyden, as a non-inflammatory process. He advocates that all affections of the kidney, which are of a degenerative nature but not inflammatory, should be designated as "nephrosis," in which there is degeneration of the tubules, but no demonstrable changes in the glomeruli or vessels. He also adheres to Volhard's classification of the nephropathies into focal nephritis (infection), true nephrosis, sclerosis, and diffuse glomerulonephritis. In the nephrosis of pregnancy the excretion of water is delayed according to Von Jaschke; although the urine concentration tests show no impairment. This means that

there is a disturbance in water secretion outside of the kidney, and is due to inability of the water to reach the kidney, because of an abnormal permeability of the vessels. He also thinks that a toxin, which acts on the endothelium of the vessel walls, causes epithelial degeneration which results in the increased permeability.

Both Von Jaschke and Volhard are of the opinion that in addition to this degenerative process, with oedema but without hypertension, known as nephrosis, there also occurs a form which is liable to lead to eclampsia, and which presents the picture of typical diffuse glomerulonephritis. In the latter type of kidney disease there is hypertension and marked oedema. Baer thinks that the "kidney of pregnancy" occupies a place between nephritis and nephrosis and that the initial changes probably occur in the renal-vascular system. This author used functional tests in order to differentiate between the various types of renal disease. One of them consists in determining the changes in the specific gravity in a series of two hourly specimens of urine, with the object of ascertaining the functional activity of the tubular system. Another test is aimed at evaluation of the functional activity of the glomerular system. In a normal person an extra litre of water taken at any one time, will be excreted in less than four hours; while in nephritis there is definite delay in excretion. Baer concludes that nephrosis and nephritis are separate entities, involving different portions of the kidney tissue, and that it is possible by means of the two tests just mentioned, aided by capillaroscopy, urinalysis and blood pressure readings to differentiate between nephrosis and nephritis complicating pregnancy, and he believes that the prognosis is better in the former than in the latter.

Heynemann also differentiates between nephrosis and nephritis during pregnancy, and states that the histology of the eclamptic kidney is that of nephrosis (degeneration of tubules and glomeruli) and not a nephritis or an inflammatory process. He thinks that the nephrosis of pregnancy is really a glomerulonephrosis, and that healing in such conditions is quick and complete, and that such patients may go through subsequent pregnancies without further trouble. This author regards it a simple matter to differentiate between eclampsia and uremia complicating pregnancy, although there are no sure differential signs. A marked increase in blood pressure, the appearance of

erythrocytes in the urine and an albuminuric retinitis appearing in the second half of pregnancy are indicative of nephritis; and should the same signs appear in the first months of pregnancy, the condition must be considered as chronic nephritis.

At the present time, while our knowledge of nephritis complicating pregnancy is still quite meagre, it appears to the author that the use of the term "nephrosis," in classifying the toxemias of pregnancy, serves no useful purpose. By it is understood a mild degenerative tubular process, and it seems doubtful whether we are as yet able to diagnosticate a "nephrosis" during pregnancy. In our estimation, the term merely serves to cloak our ignorance and to obscure still further our knowledge.

In this paper the following classification will be used:

1. Vomiting of pregnancy
2. Low reserve kidney.
3. Nephritis complicating pregnancy
4. Pre-eclampsia
5. Eclampsia
6. Acute yellow atrophy of the liver

Low reserve kidney is probably identical with "kidney of pregnancy," with certain types of "recurrent pregnancy toxemia," with the simple "albuminuria of pregnancy" as well as with certain of the "nephroses" of pregnancy. The author is of the opinion that it is frequently impossible, especially when the patients' previous history is unknown, to differentiate between the various types of kidney diseases during the course of pregnancy, such as the acute and chronic nephritides and nephroses; and he is fully aware that the above classification, which he has suggested and will follow in all subsequent discussions, is tentative and perhaps inadequate, awaiting the discovery of the etiology of certain of these toxemias of pregnancy. This classification has been followed at the Johns Hopkins Hospital for the past three years and has proved fairly satisfactory, as less than five per cent of the patients suffering from a toxemia of pregnancy were placed in an "unclassified" group.

I. Vomiting of pregnancy

Vomiting occurs in approximately 50 per cent of all pregnancies, appearing at about the fifth or sixth week and lasting from six weeks to two months. Fortunately, in the majority of cases the vomiting is slight and we may speak of it as "morning sickness." According to Pick, vomiting of pregnancy may proceed to the pernicious stage in about one in every 1000 pregnancies. Williams is of the opinion that pernicious vomiting occurs more frequently, and that it is encountered once in 700 pregnancies among women of the upper classes in this country. It seems to be the general opinion that pernicious vomiting of pregnancy is more prevalent in the United States and France than in Germany and England.

It is generally stated that Soranus, in the latter part of the first century, was the first to describe the disease, but it was not until the nineteenth century that its importance was fully appreciated. In 1879 Matthews Duncan pointed out that pernicious vomiting is sometimes associated with definite liver lesions; and Williams, Ewing and Stone have directed attention to what they consider a characteristic type of liver lesion in severe cases of pernicious vomiting. Necrosis takes place in the central portion of the liver lobule, quite contrary to the usual findings in eclampsia. Instead of hepatic necrosis, marked fatty degeneration of the liver lobules may make its appearance. It is questionable if we are justified in speaking of a typical liver lesion of vomiting, because in the cases, that have been studied in the post mortem room, there have been superimposed the effects of marked starvation and dehydration, which in themselves produce typical histological changes. Because of the nature of the disease, we shall undoubtedly have to resort to animal experimentation to formulate a true concept of the pathological findings associated with vomiting of pregnancy.

It has been the custom to regard vomiting of pregnancy as of three separate and distinct types; (1) reflex vomiting (2) neurotic vomiting and (3) toxemic vomiting. Williams states that the neurotic is the most, and the reflex the least frequent type, and that toxemic is the most serious. Not all writers agree with this classification, some believing that vomiting of pregnancy is always due to neurosis, while others hold to a toxemic basis in every instance. After a discussion

of the work on the etiology of the disease, we shall return to the question of classification.

Etiology. There have been numerous theories concerning the etiology of vomiting of pregnancy. Tweedy believes that absorption of food particles during the early stages of their digestion is responsible for hyperemesis and that in early pregnancy a foreign element appears in the blood, and the normal food anti-bodies are thereby interfered with. Tweedy considers the vomiting of early pregnancy as Nature's effort to reject food incapable of proper neutralization. Siegert, on the other hand, believes in hunger as the cause of vomiting.

Levy-Solal attempted to discover whether women, suffering from vomiting of pregnancy, are sensitive to placental extract, and found that in the placenta of a vomiting patient there is an antigen which is reactivated by human serum and which produces shock in guinea pigs; this antigen is not present in young normal placentae, and at the end of pregnancy the placenta is also without such an antigen. He came to the conclusion that women with vomiting of pregnancy are sensitive to placental extract, and that after abortion they remain sensitive two to three days. After the fourth month of pregnancy these patients are no longer sensitive to such an extract. On the assumption that a toxin produced by the foetus or placenta is the cause of vomiting of pregnancy, Mack suggested the use of serum from normal cases of advanced pregnancy in the treatment of these patients, believing that the normal cases must have become immune to these toxins.

Hirst argues that every woman during her menstrual life is constantly absorbing corpus luteum substance, but that with the onset of pregnancy this absorption ceases. The corpus luteum of pregnancy increases in size until it reaches its maximum in the third month of gestation, and from this time on it is gradually absorbed. He calls attention to the fact that the vomiting of pregnancy disappears at about the time that the corpus luteum begins to decrease in size, and suggests that this is not a mere coincidence but that the corpus luteum plays an important part in relation to vomiting. With this idea in mind he has developed a treatment for vomiting of pregnancy which consists in administering corpus luteum extract.

Some authors believe that the neurotic element plays an important part in hyperemesis. Both Schwab and Lynch are of the opinion

that most cases of the vomiting of pregnancy can be explained on the basis of an underlying neurosis. Brindeau is also a firm adherent of the hysteria theory for the etiology of vomiting.

Heinrichsdorff, as a result ,of his studies in a large series of cases, regards hyperemesis as a typical disease of the first half of pregnancy in which it is often impossible to determine any organic disease. In many cases death may ensue and a post mortem reveal nothing positive. This author feels that hyperemesis is not derived from an intoxication, but that it becomes transformed into such. Kotz finds an over irritability of the vagus an underlying factor in most cases of vomiting, while Seitz thinks that it is due to reflex, psychic and toxic vagal-stimulation, and that the vagal changes may be caused by disturbances of inner secretion.

Ferru is of the opinion that hepatic insufficiency in severe cases of vomiting of pregnancy is not the pathological cause, nor is it of great prognostic value, as is usually believed. It is the consequence and not the cause of vomiting according to this author. Sella regards insufficient ovarian activity as the cause, while Silvestri, Rebaudi, Sergent and Rathey think that in insufficient adrenal and poly-grandular activity one may discover the cause of vomiting of pregnancy.

In 1919 Harding and Duncan advanced the theory of glycogen deficiency in the liver of the mother as the cause of vomiting of pregnancy. They came to this conclusion because most patients suffering from vomiting of pregnancy showed ketonuria, and because these patients improved on a diet rich in carbohydrates. Since the appearance of the paper of these two authors a great deal has been written about carbohydrate deficiency in vomiting of pregnancy. Titus believes that the carbohydrate deficiency theory is the chief underlying factor in the causation of the vomiting of pregnancy as well as that of the other toxemias.

Adair states that vomiting of pregnancy conforms to no particular type and is not dependent on the taking of food and very often food is not vomited. He further calls our attention to the spongy bleeding gums, salivation, peculiar odor of the breath, epigastric distress, hematemesis and constipation, that may accompany the vomiting.

From a general consideration of these various theories concerning the etiology of vomiting of pregnancy, it seems most likely that a

metabolic disturbance, and in particular, perhaps, an upset in the carbohydrate metabolism which in turn leads to incomplete oxidation of fatty acids, plays a rôle in the different manifestations of this toxemia of the early half of gestation. These metabolic disturbances will be more fully discussed after we have considered the chemical changes accompanying this disease. Failure on the part of the mother to destroy foetal tissue that had entered the maternal circulation may be a further factor.

Urine and blood. In vomiting of pregnancy, the analysis of the urine does not show any marked disturbances of the nitrogen partition, except in very severe cases when we notice an increase in the ammonia coefficient. Williams was the first to observe this change in the nitrogen partition, and for a time regarded all patients suffering from vomiting of pregnancy with an ammonia coefficient of 10 or over as severely sick. Underhill and others, however, have shown that a high ammonia coefficient may be the result of simple starvation, and Williams endorses this view. Drennan and Hicks believe that there are two types of vomiting of pregnancy; the neurotic and the toxic; in the neurotic type of hyperemesis there is no increase in the ammonia coefficient in the urine, while a marked increase always accompanies the toxic type.

In a very careful study of the metabolic changes in vomiting of pregnancy, Dieckmann and Crossen could find no marked disturbances in the urinary components, except for a decrease in the chlorides. According to Stander, Duncan and Moses the excretion rate of urea is within normal limits. Cleisz and Laudat came to a similar conclusion. We may therefore conclude that analysis of the urine in vomiting of pregnancy has revealed no outstanding differences from the normal, except a high ammonia coefficient, which is probably the result of starvation.

Examination of the blood components has given us more specific information. According to Stander, the non-protein nitrogen and uric acid are usually increased in severe cases of vomiting of pregnancy. Harding and his coworkers, as well as Haden and Guffey, found in addition to an increase in non protein nitrogen and uric acid, an increase in urea. These authors also reported low values for sodium chloride. Harding regards the decreased chlorides as indicative of

dehydration. Dieckmann and Crossen report normal or occasional increased non-protein nitrogen and urea nitrogen and increased uric acid in the blood. Killian and Sherwin found increased non-protein nitrogen but decreased urea nitrogen in pernicious vomiting. The increased uric acid noted in their cases of vomiting of pregnancy they ascribe to an impairment of renal function. Plass and his coworkers have studied the partition of the nitrogenous products in the blood stream in the different forms of pregnancy, both normal and abnormal, but could find no significant changes in the protein fractions in vomiting of pregnancy.

Runge and Juhl report increased amino acids in vomiting of pregnancy. In normal non-pregnant women they found 27.3 mgm. per cent; in normal pregnant women 32 mgm. per cent and in cases of vomiting of pregnancy from 45 to 76 mgm. per cent. Increased lactic acid in the blood has also been observed by Loeser.

The blood sugar in vomiting of pregnancy has received a great deal of attention. Dieckmann and Crossen, in their very careful study of a large number of cases, reported that the blood sugar is within normal limits. Most authors have found this to be the case. Titus, on the other hand, believes that there is a hypoglycemia in vomiting of pregnancy, and he goes so far as to assume that this hypoglycemia is associated with the etiology of the disease. In this clinic we have been unable to substantiate Titus' findings and observe normal blood sugar values in vomiting of pregnancy. The sugar tolerance test has been used to determine the existence of any disturbance in the carbohydrate metabolism during pregnancy. Kermauner is of the opinion that in severe cases of vomiting there is a disturbance in carbohydrate metabolism, which is manifested by an abnormal sugar tolerance.

Bokelmann and Bock noted a marked increase in "acetone bodies" in 22 cases of vomiting of pregnancy. They divided their cases into three groups: (1) physiologic vomiting, in which the amount of acetone bodies in the blood is below 80 mgm. per 100 cc. of blood; (2) emesis gravidarum, in which there is more than 100 mgm. of acetone bodies per 100 cc. of blood; and (3) hyperemesis gravidarum, in which the concentration of acetone bodies in the blood is over 150 mgm. per 100 cc. They further believe that when the acetone bodies in the blood is 200 mgm. per 100 cc. of blood, we are dealing with a malignant form

of the disease. According to these authors, the increase in acetone bodies is due to an actual shortage in carbohydrates, a deficient metabolism of carbohydrates and a change in the fat metabolism. Vomiting of pregnancy leads to undernutrition and this in turn to decomposition of body substances. Rubner has shown that on maintenance diet there is only about 7 per cent more energy used than in hunger. With longer starvation, and after the carbohydrates have been exhausted, the fats and proteins of the body are called upon to furnish the required energy. In relative starvation the energy consumed probably follows the same principle as in actual starvation, protein being spared to the very last. While the protein is being spared, the fat is used up, and as a result of this increased burning of fat, the fat content of the blood increases and acetone bodies appear in the urine. Small amounts of glucose given in starving animals are enough to start a great amount of acetone bodies in the urine, and consequently an acetonuria follows more as a consequence of carbohydrate deficiency than as a result of inanition.

Ketosis, or an increased production of acetone bodies, may be induced in a normal individual by the ingestion of a salt-free or a carbohydrate-free diet. The complete oxidation of fatty acids depends on an ample supply of carbohydrates or antiketogenic substances. The ketogenic-antiketogenic ratio has not been carefully studied in vomiting of pregnancy, and it is probable that such an investigation may reveal a ratio exceeding the normal limits.

The acid-base equilibrium seems to be undisturbed in vomiting of pregnancy. Dieckmann and Crossen found even in severe cases of pernicious vomiting the hydrogen-ion concentration as well as the CO_2-combining power (compensated alkali deficit) to be essentially normal. Harding and Stander also report normal values for the plasma CO_2-combining power.

The most outstanding chemical changes, therefore, accompanying severe vomiting of pregnancy are a high ammonia coefficient in the urine, slightly increased non-protein nitrogen, decreased blood chlorides, and increased uric, amino, and lactic acids, with a marked accumulation of acetone bodies in the blood stream. Dehydration, starvation and incomplete oxidation of fatty acids following a high ketogenic-antiketogenic ratio, undoubtedly play the important rôle in the production of these chemical changes.

Treatment. As an outcome of the theory of Hirst that the corpus luteum plays an important part in relation to vomiting of pregnancy, extract of corpus luteum has been extensively used in the treatment of this disease. Hirst has reported a large number of cases successfully treated with this extract. Quigley reported 17 cases so treated, of these 12 were permanently cured, 4 improved and 1 not benefited. Coffey reports unsatisfactory results with dry extracts of corpus luteum, whereas good results followed the use of hypodermic injections of corpus luteum solutions.

Cary has employed the desiccated placenta in treating vomiting of pregnancy. He reports 13 cases with satisfactory results in 11. This author agrees that, if vomiting of pregnancy is due to a lowered immunity to the syncytium, as seems probable by the work of Acconi, the desiccated placenta may stimulate by acting as an antigen; and if the proteolytic ferment is lower, the desiccated placenta may increase the ferment content of the blood. He also believes that the placenta may be a gland of internal secretion, and so may activate the thyroid and adrenals and thereby hasten the oxidation of partially split products of protein which may be thrown into the blood stream.

According to Garnett, pernicious vomiting is probably a development of physiological vomiting of pregnancy, due to failure of the patient to produce a hormone antagonistic to the toxemia. He believes that the vomiting is caused by a poison and that the only satisfactory treatment so far developed consists in transfusion from post partum patients. This treatment has been used by others but with unsatisfactory results.

Pougert reports 4 cases suffering from pernicious vomiting and treated with their own blood. Corpus luteum and adrenalin were of no avail and after the patents had become very seriously ill, they received 20 cc. of their own blood mixed with 2 cc. of sodium citrate, and improvement followed.

Lynch is of the opinion that the formation of the nervous habit of vomiting accounts for the majority of cases of vomiting of pregnancy. He therefore tries to break this habit and treat the underlying cause of hyperacidity by medication and diet. The patient is put to bed, all food and drink by mouth is stopped until there has been no vomiting for twenty-four hours. The bowels are kept open, the patient is

given large doses of bromide as well as glucose and soda by rectum. Fruits and sweets are entirely contraindicated for many days and until the diet has been extended to include vegetables. Lynch believes that his results justify this treatment. In a personal communication to the author, Brindeau of Paris writes: "In the early toxemias (uncontrollable vomiting) I believe there is always a psychiatric basis. I always treat them by isolation and I no longer practice abortion."

Oldfield places his patients suffering from vomiting on an ordinary diet. This author is also of the opinion that all cases of vomiting of pregnancy are due to a neurosis and treates his patients accordingly.

X-ray treatments have also been tried in hyperemesis without convincing results. Fraenkel, however, is impressed by the success of x-ray therapy and reports 4 cases successsfully treated by x-ray application to the stomach. Luikhart proposed the use of luminal, stating that this drug always allays nausea and vomiting, and advised that it be administered hypodermically. In his hands this drug has proved successful in hyperemesis gravidarum, when intravenous corpus luteum and glucose and duodenal feeding had failed. Sieger starves his patients for three days and then gives them calcium with Ringer or normal saline solution together with bromides for the nervous system.

Duodenal feeding has been one of the recent methods of treatment. Haddock believes that the principle indication for the use of the duodenal tube is the loss of weight due to starvation or dehydration of the tissues. Schaick, on the other hand, thinks that the administration of water is the most important medication and that by supplying large amounts of water which is rapidly absorbed in the intestines, the patient usually gets well.

Davis reports a large series of patients suffering from vomiting of pregnancy treated quite successfully. His treatment in part is as follows:

"A careful history will usually reveal any previous gastrointestinal disturbance, or other physical conditions which might make the patient more sensitive to the disturbed metabolism of pregnancy. The physical examination will reveal any source of local irritation or infection. Drain the pus pockets or remove infected tonsils if necessary. Dental work must not be neglected during pregnancy. Try to correct a uterine displacement.

Treat acute cervicitis when present. Any of these may increase the nausea and vomiting, but are regarded as predisposing rather than causative factors.

"Cases approaching the pernicious stage require a special nurse and should be in a hospital. If seen early before marked dehydration and severe acidosis develops, stop all food and liquid by mouth and give 2 to 5 per cent glucose solution per rectum. Two hundred and fifty cubic centimeters of the glucose solution containing from 30 to 60 grains each of sodium bromide and sodium bicarbonate may be given as a retention enema every four or six hours. As the nervousness is controlled reduce the bromide to 30 grains. After twenty-four or thirty-six hours the patient may be allowed very small amounts of fluid and later solid food by mouth.

"Severe cases seen after marked dehydration is present should have 800 to 1000 cc. of N/NaCl under the breasts. If possible, should have an 18 or 20 per cent glucose solution in triple distilled water intravenously."

Since the work of Duncan and Harding in 1919 on the effect of high carbohydrate feeding in vomiting of pregnancy, there has developed a wide spread interest in the use of carbohydrates in the treatment of this disease. Thalheimer advocates the use of insulin in the treatment of vomiting of pregnancy. He first used insulin in combating the acidosis following operations and then extended its use to the treatment of pernicious vomiting. He has reported some excellent results with the use of insulin. Following the work of this author, insulin has been extensively used in combating this toxemia. It is customary to give a protective dose of glucose with the insulin. It seems that this combined therapy of insulin and glucose relieves the ketonuria and acidosis, which usually accompanies vomiting. Thalheimer argues that there is a vicious cycle of acidosis causing vomiting and that the starvation following the vomiting causes further acidosis of a starvation type. He thinks that insulin breaks this cycle by enabling the body to oxidize the glucose, which in turn causes the burning of the products of incomplete fat metabolism, such as acetone, diacetic acid and B-oxy-butyric acid. Insulin and glucose have been used in many clinics and very satisfactory results have been reported. Titus, on the other hand, is of the opinion that glucose alone gives better results than insulin and glucose, and there has been quite a controversy in the literature as to the relative merits of these two methods of treat-

ment. Bokelmann agrees with Titus that insulin is a dangerous drug to be used in the toxemias of pregnancy.

Other German authors, however, such as Loeser, strongly advocate the use of insulin and glucose.

Vogt states that in vomiting and in eclampsia, as in hunger, there is glycogen starvation with increase in acetone bodies, a result of lack of carbohydrates or an abnormal metabolism of carbohydrates. The disturbance of carbohydrate metabolism is associated with a disturbance in protein metabolism, which shows an increase in ketone bodies and uric acid. He consequently uses insulin and glucose in the treatment of vomiting of pregnancy, believing that insulin alone is dangerous.

Mussey advocates a diet high in carbohydrates and a high fluid intake, with sufficient sedatives to raise the threshold of nervous irritability. In patients who show a low gastric acidity, he advocates the use of dilute hydrochloric aid, and in severe cases of vomiting intravenous injections of dextrose solution, together with insulin. Falkins is of the opinion that all women suffering from vomiting of pregnancy are undernourished and that it is possible to prevent vomiting in most cases by dietary measures. He consequently advocates increased carbohydrate nutrition.

The author has seen most of the methods enumerated above tried, and is convinced that there are a few cases which do not respond to any of these methods of treatment. There is undoubtedly a toxemic basis for vomiting of pregnancy, although the neurotic element should not be overlooked. From a clinical study and the chemical findings in the urine and blood, as well as from experimental work on animals, it seems to the author that all cases of vomiting of pregnancy are based on an underlying toxemia. In some women this toxemia may be so obscured by a predominating neurosis that one is almost entitled to make a diagnosis of neurotic vomiting. There is such a profound change in the metabolism during the early months of pregnancy that one might expect a certain percentage of patients to respond abnormally to this changed metabolism. We know that the foetus must get its food supply, and particularly its carbohydrates and protein, from the mother. From the work on the respiratory quotient of the foetus by Murlin, Stander and others, it is fairly well established that the

foetus utilizes mainly the carbohydrates for its energy requirements. This undoubtedly means a drain on the maternal carbohydrates, as is shown by the work of Bokelmann and his coworkers. The marked accumulation of acetone bodies must mean a profound disturbance of carbohydrate and fat metabolism. There can be little doubt that the changed metabolism accompanying pregnancy, which may so easily become perverted, as shown by the tendency towards acetonuria in pregnant women (Novak and Porges and others), is the underlying cause of all cases of vomiting of pregnancy. Apparently we do not know the starting point of this changed metabolism, but it seems rational that in the treatment we should endeavor to restore the patient to a normal metabolism. So far the best therapy to this end seems to be the use of insulin and glucose. When the vomiting has persisted to the extent of dehydration, and it is apparent that the tissues are urgently in need of water, one must undoubtedly immediately administer water, either in the form of saline or glucose solution intravenously, or by infusion, or by rectum.

When called to see a patient suffering from vomiting of pregnancy it is essential first to determine the severity of the disease, and whether starvation and dehydration have entered into the picture. If we are dealing with the results of starvation or dehydration or both, our therapy should be to introduce nutrition and water. If the disease has not developed to this final stage, it is advisable to determine how much, if any, neurotic element is involved and to treat the patient accordingly. It is of course essential that a careful clinical examination of the patient be carried out, in order to determine the presence or absence of such gynecological conditions as retroversion of the uterus, which, when present, should receive attention. Often the correction of such conditions leads to improvement.

As far as treating the actual vomiting of pregnancy is concerned, the author is of the opinion that the use of glucose or glucose and insulin, where indicated, and the administration of small but frequent meals, gives fairly satisfactory results. It is often advisable to starve the patient for twenty-four hours before instituting the therapy, and it is always necessary to enforce strict isolation. However, we must remember that in a small percentage of cases all therapy may be of no avail and a therapeutic abortion is inevitable. It must be pointed

out that we cannot lay too much stress on the value of complete isolation of the patient, especially from all relatives, and of suggestion.

II. Low reserve kidney

Though the term "low reserve kidney" may be inadequate and inaccurate, nevertheless, it describes a certain group of pregnancy toxemia cases perhaps as well as any other appellation so far suggested. In this group are incorporated many cases of "albuminuria of pregnancy." Albuminuria accompanies most of the toxemias of the latter half of pregnancy and it therefore appears both illogical and confusing to attempt to designate any one type of toxemia as "albuminuric." It is analogous to speaking of a "hypertensive" type of toxemia since the majority of women suffering from the various late toxemias of pregnancy have an elevated blood pressure. The term "albuminuria" should be reserved to denote a laboratory finding and no more. If this rule be followed in the future, it will not be such an impossible task, as it now is, correctly to interpret the meaning of the many authors using this word.

There is more justification for the use of the designation "recurrent toxemia." The only objection to it is that it does not tell us whether the process is benign or will become progressively worse with subsequent pregnancies. Either condition may be recurrent, but it is a matter of great importance for the physician to know whether the patient is suffering from a mild and benign toxemia or from a kidney condition which, if treated inadequately, may prove fatal in the near future. Furthermore, even eclampsia may be "recurrent." For these reasons the use of the term "recurrent toxemia" may be somewhat confusing to some of us.

Nephrosis as seen in the non-pregnant individuals, is a fairly definite entity and usually signifies a degenerative change in the tubules of the kidney. Mussey and Keith divide the acute nephritis occuring during pregnancy into acute glomerulonephritis and acute nephrosis, and state that while the former is associated with hypertension, oedema, oliguria and albuminuria, the latter differs from it in the absence of hypertension and changes in the fundi, and usually in the absence of erythrocytes in the urine and in the presence of oedema. From a clinical

and laboratory study, involving fairly complete urine and blood analyses, as well as kidney function and urea-excretion tests, of all toxemic patients in the Woman's Clinic of Johns Hopkins Hospital during the past six years, it appears to the author that we are not yet in a position to differentiate between acute glomerulonephritis and acute nephrosis occurring during pregnancy. It is for this reason, as stated earlier in this paper, that, in classifying kidney lesions associated with pregnancy, we believe the word "nephrosis" should be reserved until more is known about the behavior of the kidney during gestation.

This brings us to the term "low reserve kidney." It was only by studying repeated pregnancies occurring in the same individual that Stander and Peckham were able to differentiate the low reserve kidney from the other types of toxemias. This is the mildest form of late toxemia of pregnancy and usually manifests itself during the last two months of gravidity. These authors give the following as characteristic criteria:

"1. An elevated blood pressure, which at the end of the puerperium has dropped to a normal level. In most instances this elevation is not very marked, rarely exceeding 150 systolic and 90 diastolic.

2. The amount of albumin in the urine is never very great, varying before delivery between a fraction of a gram and 2 grams per liter, although the lower figures are most usually observed. The albumin disappears during the puerperium, and the patient leaves the service either with no albumin at all, or with at the most 0.1 gram per liter.

3. The outstanding characteristic is the fact that in subsequent pregnancies, the patient's condition does not become aggravated, and she is as well as, or better than, she was in the preceding pregnancy. Each of our 14 cases clearly demonstrates this point.

4. The blood chemistry as well as the urinary analysis reveals nothing abnormal.

That the number of pregnancies through which the individual may go plays any rôle in the development of this entity is very doubtful, for the reason that we observe it in primipara as well as in all degrees of multiparity. Moreover, this type of kidney does not seem to be permanently injured by pregnancy. As the woman approaches term a certain amount of albumin may pass through the glomerular membrane, the blood pressure become elevated, and some edema develop. With regard to the latter point it is interesting to note that in subsequent pregnancies there may be either no edema or at the most a slighter degree than before.

It is well known that in a healthy person, under normal conditions, all of the glomeruli are not functioning at capacity at any one time, and it has been estimated that there is usually a margin of safety which approaches 50 per cent. In other words, there is a decided kidney reserve which may be called into play. It therefore, seems resonable to suppose that in certain individuals such kidney reserve may be greatly decreased, due either to congenital causes or to factors which may have lessened the number of functioning glomeruli without producing a chronic nephritis. As we shall see in another group of cases, the strain of pregnancy always aggravates a chronic nephritis, so that later the kidneys are less well prepared to stand the strain of subsequent pregnancies. In the type of kidney under consideration this is not the case. All we can say is that the kidney reserve seems to be too low to meet the extra demands of pregnancy, as is manifested by the passage of a certain amount of albumin through the glomerular epithelium and by a moderate elevation of blood pressure, and that these manifestations usually disappear completely within two weeks after delivery. Furthermore, the kidney substance does not seem to have been injured by the pregnancy and the kidney reserve is certainly not lower in subsequent pregnancies. Such kidneys appear to be quite capable of functioning adequately while the woman is not pregnant, as well as for her and her fetus until about the eighth month of pregnancy, when manifestations of the low reserve kidney begin to make their appearance.

In addition to the 8 cases in our original paper, we have been able to find six more patients, who, during the period studied, had had a pregnancy with the typical signs and symptoms of a low reserve kidney, followed subsequently by a normal pregnancy. Such observations may be regarded as indisputable evidence that the occurrence of a mild toxemia in a given pregnancy is not necessarily followed by trouble in a subsequent one, and would accordingly indicate that the kidneys had not been permanently damaged."

The author proposes that this type of toxemia of the latter half of gestation be classed in our obstetrical clinics as "low reserve kidney" or as "recurrent toxemia," limiting the latter term strictly to the type of cases described in the preceding paragraphs. For the sake of uniformity this group will be referred to as low reserve kidney throughout all subsequent discussions in this paper.

Incidence. In this clinic in 253 women suffering from pregnancy toxemia during the years 1926 and 1927, low reserve kidney constituted

35 per cent of the total number. Likewise, a study of the histories of all toxemic patients treated in this Department since 1897 gave further evidence that from one fourth to one third of them suffered from this mild type of toxemia. Formerly a considerable proportion of patients with low reserve kidney were grouped as pre-eclamptic, and a smaller proportion as nephritic. From a study of the past history, blood pressure, urine-albumin, presence or absence of oedema, urine and blood chemistry, eye grounds, symptomatology and the duration of pregnancy, it is usually possible to make a correct differential diagnosis between low reserve kidney, chronic nephritis complicating pregnancy, and pre-eclampsia. This differential diagnosis will be disussed in detail after these other two types of toxemia have been considered.

Each year approximately 3 per cent of our toxemic patients fall into an unclassified group because the data at the time of discharge from the ward are insufficient for purposes of classification. In low reserve kidney the elevation of blood pressure and the albuminuria usually disappear completely two weeks after delivery, but in a very small fraction of cases it requires four to six weeks before the blood pressure becomes quite normal and the urine albumin-free.

As it is apparent that the outstanding manifestations of this toxemia are a slight elevation of blood pressure and a mild albuminuria it is advisable that we review some of the work on hypertension and albuminuria in pregnancy.

Hypertension and albuminuria. A slight elevation of blood pressure appears in a small proportion of all normal pregnancies. Irving studied the systolic blood pressure in 5000 consecutive cases of pregnancy, at the Boston Lying-In Hospital, and found that in 80 per cent the systolic blood pressure ranges between 100 and 130, and in 9 per cent falls below 100. In 11 per cent of his cases the blood pressure was 130 or over. This author believes that age, nationality and parity have an influence on the blood pressure; and that in the young person a high blood pressure is more frequently a sign of toxemia than in women over thirty years of age. His figures also show that an elevated blood pressure is more frequently an index of toxemia than is albuminuria, and is also an earlier sign.

Furthermore, the degree of elevation of blood pressure is of more significance than the amount of albumin in the urine, although both

are of great importance. Schulze states that the normal range of blood pressure during pregnancy is between 100 and 130 and that a systolic blood pressure of 150 or over should be regarded as an index of toxemia.

Donaldson studied the blood pressure in normal and abnormal pregnancy and came to the conclusion that during normal pregnancy there is no increase in blood pressure, nor does any fall in blood pressure occur immediately after labor. In cases of albuminuria complicating pregnancy, the most startling feature is the high systolic blood pressure.

Williamson states that hypertension may exist throughout pregnancy with no apparent sign of kidney disease. He believes that this type of hypertension is probably of vascular origin, caused by some toxic substance acting on the arterial wall. According to this author the prognosis in these cases is grave. Corwin and Herrick made a study of 165 cases of subacute or hypertensive type of toxemia of pregnancy, and found that 74 per cent showed cardiac hypertrophy, sclerosis of the brachial or radial arteries, vascular eye changes, or persistent elevated blood pressure after a period of from six months to six years post partum; and of these over one third showed persistent hypertension. Their investigations furthermore proved that in subsequent pregnancies the majority of women suffering from this type of toxemia will again exhibit hypertension, and they advise that such women should be observed over a series of years for evidence of cardiovascular disease.

Kylin in an extensive review of the question of hypertension divides all cases into two groups. To the first group belong acute diseases, such as glomerulonephritis, essential hypertension and arteriosclerosis, and to the second group the chronic conditions, such as contracted kidney. Hussey has reviewed all the disturbances, which may be associated with normal pregnancy, and believes that there are toxic substances of the amine type which may act upon the walls of the blood vessels, and that these substances have their origin in the placenta and perhaps also in such glands as the pituitary. Volhard has also described similar substances as sensitizing the vessel walls, making them particularly sensitive to pressor bodies. Hussey believes that these amines have a widespread action and that oedema is generally due to damage to the capillary walls resulting from the activity of these amines.

De Snoo groups the hypertension incident to gestation as follows: (1) hypertension associated with toxemia, (2) hypertension resulting from chronic nephritis, and (3) essential hypertension. His first group undoubtedly includes cases of low reserve kidney, as well as pre-eclampsia. The hypertension of chronic nephritis will be discussed later. Often we notice an elevated blood pressure without any other signs of toxemia. It is usual to regard this condition as essential hypertension. Essential hypertension is an idiopathic condition and we know very little or nothing about its etiology. If the patient had an elevated blood pressure without demonstrable disease before she became pregnant, it is probable that she is suffering from essential hypertension. On the contrary if her pressure is normal until about the middle of pregnancy and then begins to rise, it is undoubtedly due to a toxemic condition directly associated with the pregnancy and is not an essential hypertension. A great deal has been done concerning the therapeutic action of ions in the management of hypertension. Potassium sulphocyanate and iodine have given excellent results in lowering this type of high blood pressure.

Mussey and Randall agree with Irving that hypertension, especially in women under thirty years of age, is a better index of early toxemia than is albuminuria. They state that more than 25 per cent of primiparous women have a blood pressure over 140, and that such hypertension is a fair index of the onset of a toxemia. Wallich regards hypertension in pregnancy as related to functional disturbances of the kidney and autointoxication; this type of hypertension is accompanied by headaches, oedema, insomnia and polyuria, and may be responsible for placental hemorrhage.

Ginglinger divides all cases of albuminuria during pregnancy into four groups: (1) an unimportant group with only slight albuminuria; (2) albuminuria with little, if any oedema or hypertension; (3) albuminuria with much oedema and hypertension and (4) albuminuria without much oedema or hypertension but with marked nitrogen retention. For this classification we must know the percentage of albumin and the casts in the urine. Estimation of the chloride retention is judged by the amount of oedema, daily weight of the patient, the intake and output of water, the blood pressure and the blood urea.

Haffner examined the urine in 400 cases of pregnancy, and albumin

was found in 73 cases, or about 17 per cent. DeLee states that with the nitric acid test albumin will be found in only 3 to 5 per cent of gravidae, while it is far more frequently seen during the puerperium.

Pinard and Varnier believe that albuminuria is too often blamed on the state of pregnancy, whereas it may often be due to syphilis. They report cases of albuminuria during pregnancy where anti-syphilitic treatment caused the albumin to disappear from the urine. Cook suggests that the albuminuria of pregnancy may be due to mechanical pressure and resulting hyperemia, especially of the left kidney, but he has not been able to prove this. He calls attention to the post mortem findings and requests that we pay more attention to the vascular factors. According to Cattaneo the degree of azotemia and the salt content of the blood are of greater value in the diagnosis and prognosis of pregnancy nephropathies, than the albumin content of the urine.

Tangberg relates a case of albumosuria, in the seventh month of pregnancy. The patient had felt ill during the entire period of gestation. On admission there was no ablumin in her urine, her symptoms became worse and oedema and oliguria developed with albuminuria. Diet proved of no avail, and a few days later she gave birth to a still born infant, and all her symptoms immediately improved. The urine on admission, although containing no albumin, gave a positive test of albumose; and while the albumin disappeared from the urine on the 4th day postpartum, the albumose persisted until the tenth day postpartum. No extensive work has been done on the albumoses in the urine of pregnant women, and this may well be a fruitful field for future investigations.

For a long time it has been stated that placenta praevia and premature separation of the placenta may be associated with albuminuria and toxemia. Young and Miller reported that they found albuminuria in five of ten consecutive cases of placenta praevia and there were other symptoms of toxemia in three of the remaining five. They feel that the association between placenta praevia and toxemia is much more common than is at the present supposed. Danby suggests that the extensive extravasation of the blood into the pelvic tissue may be a manifestation of toxemia. He believes that the many hemorrhages which are almost pathognomonic of toxemia are due not only to in-

creased blood pressure but also to changes within the blood vessel walls, dependent upon a toxic substance producing the toxemia.

To summarize, low reserve kidney manifests itself in about 5 per cent of all full term pregnancies. It is a mild toxemia of the latter half of gestation, not associated with permanent or progressive injury of the kidneys, and not preceded by any renal damage. This toxemia may or may not reappear in a subsequent pregnancy, and if it does it is usually not more severe. The diagnosis is made on a moderate rise of blood pressure, usually about 150 systolic and 90 diastolic, and a relatively small amount of albumin in the urine, ranging from a fraction of a gram to 1 gram per liter of urine. These manifestations of toxemia appear during the last few months of pregnancy. There may also be some oedema, and very rarely a complaint of headache. Of great importance in establishing the diagnosis is the fact that by the end of the puerperium (three weeks after delivery) the blood pressure has resumed its normal level, the urine is albumin-free, and any oedema that may have been present, has disappeared. At no time do the blood constituents show any abnormality, and the nitrogen partition in the urine is normal. In subsequent pregnancies a similar picture may recur or the patient may be entirely normal. As to the etiology of this mild form of toxemia we are still in the dark.

Rest in bed and a low-protein diet will usually prove ample treatment for these patients. Occasionally oedema of the ankles and legs will disappear more rapidly after the restriction of salt in the diet. Improvement generally follows this type of treatment, and interruption of the pregnancy is not indicated. If, however, the condition becomes worse, notwithstanding rest in bed and proper dietary measures, we are most probably dealing with a chronic nephritis and not a low reserve kidney, in which case treatment may have to be more radical.

III. Nephritis complicating pregnancy

Many attempts have been made to classify the nephropathies of pregnancy. Perhaps the most generally used terms are chronic nephritis complicating pregnancy and nephritic toxemia. Acute glomerulonephritis, chronic glomerulonephritis, glomerulonephrosis, acute nephrosis (nephrosis), acute nephritis, chronic focal nephritis,

essential hypertension (benign hypertension) and malignant hypertension constitute subdivisions of nephritis. As there is such confusion in the use of some of these terms it is advisable that we clearly define each of them.

In glomerulonephritis the lesion is primarily limited to the glomeruli, resulting in hypertension, oedema, albuminuria, oliguria, hematuria and sometimes visual disturbances. The acute form is associated with a sudden onset, usually with normal renal function except for decreased excretion of salts and water, and very slight, if any, nitrogenous retention in the blood. The chronic type of glomerulonephritis differs from the acute in that the specific gravity of the urine is low and there may be evidence of nitrogenous retention with impaired kidney function. Glomerulonephrosis is a term suggested by Fahr to denote degenerative lesions in the glomeruli.

Mueller used the word nephrosis to designate degenerative changes in the kidney in contradistinction to an inflammatory process, and it now generally signifies a primary degenerative change as opposed to arteriosclerosis. Many authors regard nephrosis as a degenerative change limited to the tubules of the kidney. The term has also been used to denote oedema and perhaps albuminuria without hypertension or impaired renal function. High lipoid and low protein content of the blood serum, together with normal fundi, are supposed to be associated with nephrosis.

Acute nephritis is a vague term and does not classify the lesion, while focal nephritis, according to Volhard, denotes slight changes in the kidney of an inflammatory nature with albuminuria, hematuria and casts, but without impairment of renal function or oedema or hypertension.

Essential hypertension, as stated earlier in this paper, is of unknown etiology and may exist for many years without renal impairment. The elevated blood pressure is the only positive finding. In the so-called malignant type of hypertension the kidneys have become involved and a secondary nephritis is superimposed on the original benign hypertension. Wagener and Keith use the term malignant hypertension to denote vascular and retinal changes without impaired renal function.

Chronic nephritis is also subdivided into parenchymatous and inter-

stitial, the former presenting three types, the large red kidney, the large white kidney and the secondarily contracted kidney. This parenchymatous type is accompanied by general anasarca, headache, visual disturbance and albuminuria; chronic interstitial nephritis is also known as primary contracted kidney and is usually associated with arteriosclerosis and cardiac hypertrophy, and is characterized by polyuria with low specific gravity of the urine, and by albuminuria.

As a rule it is impossible to differentiate between the various types of nephritis during pregnancy. The added strain of pregnancy on the kidneys tends to obscure the diagnosis of any one particular form of nephritis. As we learn more about kidney function we may ultimately be able to establish such a differentiation, but at present we must content ourselves with the general diagnosis of nephritis complicating pregnancy, unless study before its onset has made it possible to distinguish the type.

Incidence. Nephritic toxemia, or the occurrence of pregnancy in a woman already suffering from chronic nephritis constitutes about 25 per cent of all gestation toxemias. In 3,330 consecutive deliveries in the Johns Hopkins Hospital, nephritis appeared as a complication of pregnancy in 61 cases; in other words, approximately two per cent. Cruickshank investigated a series of 23,630 cases admitted to the Glasgow Royal Maternity and Woman's Hospital during a period of ten years and found that the average incidence of nephritis was 2.84 per cent.

Symptoms. In their studies upon repeated pregnancies occurring in the same individual, Stander and Peckham found the outstanding characteristics of nephritis as a complication of gestation to be as follows:

"1. The last pregnancy shows more renal involvement than the one preceding it. Usually this is shown by the fact that a rising blood pressure and the presence of albumin in the urine are noted far earlier in pregnancy than was the case in the previous pregnancy. This is true for all of our patients except one, and even in that case there was a higher blood pressure and more albumin in the urine at the end of the puerperium following the second pregnancy than after the first pregnancy.

2. The nitrogen partition in the urine is often disturbed, the ammonia nitrogen increasing and the urea nitrogen being relatively less in amount.

3. In some cases nitrogenous retention in the blood becomes quite appreciable, as is shown by a rise in the nonprotein nitrogen, as well as in the urea nitrogen.

4. Edema is quite marked in a large percentage of cases and sometimes persists throughout the puerperium.

5. At the end of the puerperium following the last pregnancy the blood pressure, especially the diastolic, has not returned to the normal level; and there is usually some albumin in the urine.

The cases in this class can probably be divided into two subgroups, namely, those who had developed a chronic nephritis prior to the first pregnancy, or between pregnancies, from such causes as scarlet fever, tonsillitis, infectious diseases, myocarditis, or any of the conditions which may lead to chronic nephritis; and those in which repeated pregnancies may have played a rôle in the development of the nephritis. The past history of the patient will prove of value in determining such relations.

It is highly important that the obstetrician determine whether or not the toxemia falls into this group, for his advice to the patient and the treatment of the pregnancy will be governed accordingly. When there are definite signs of chronic nephritis it is unwise to allow the occurrence of further pregnancies, for each subsequent pregnancy leads to an earlier 'break' in the kidneys, and to more permanent damage to the renal tissue."

Kidney function. Several tests to determine kidney function have been developed during the past few years; of these the phenolsulphonephthalein test has been the most extensively used. Sonderer and Harvey, by means of this test, estimated the renal function in normal pregnancy and found a decreased excretion of the dye in the latter months of pregnancy. In the absence of renal lesions, they believe that it is due to a disturbance in the kidney function resulting from pressure exerted by the enlarging uterus. They emphasize the fact that the amount of dye excreted is the important factor in determining the function. We have used this test routinely for several years and have reluctantly come to the conclusion that it is not of much value in chronic nephritis complicating pregnancy.

Wallis proposed the urinary diastase test and believes that it gives conclusive evidence of renal insufficiency. In nephritis complicating pregnancy, he found consistently low values; while in all other cases of toxemia in pregnancy the test gave high values, which are usually much higher than normal. Most of the work on this starch-splitting

enzyme in the urine followed the observation of Wohlgemuth in 1909 that the amount of diastase is increased in pancreatic disease. Corbett found that a certain amount of diastase is present in normal blood and is excreted by the kidneys. Damage to the kidney epithelium results in an altered excretion of the enzyme. Schaanning used the formula

$$\frac{\frac{du \times D}{15}}{d_s}$$

to denote the ability of the kidney to concentrate diastase, (du is the diastase in 1 cc. of urine, d_s the diastase in the serum and D the amount of urine in twenty-four hours). He showed that in chronic nephritis the ability to concentrate diastase is reduced. Del Piano employed the same test as an index of kidney function during pregnancy, and states that where the kidney is normal there is less diastase in the blood serum than in the urine, while in cases of kidney damage the amount of diastase increases in the blood and decreases in the urine. Sepetinskaja determined the amylase index in non-pregnant and pregnant women, and in the first half of gestation observed values within the normal non-pregnant limits in 77.3 per cent of his cases, while in the remainder the index was higher. In the second half of pregnancy he found almost similar values, 81.9 per cent normal and 18.1 per cent higher. He does not agree with Wallis that nephritis may be differentiated from pre-eclampsia by means of a diastase test.

Many tests have been based on the excretion rate of urea, and most of these have followed the laws laid down by Ambard in 1909. His first law states that the urea excretion is proportional to the square root of the concentration of urea in the blood, other factors remaining constant; and, according to his second law, if the urea concentration in the blood is constant, the rate of urea excretion is inversely proportional to the square root of the urea concentration in the urine. Walker and Rowe in experiments carried out on normal and nephritic subjects found the first law of Ambard to be correct within only certain narrow limits, and the second law to be completely invalid.

In 1914 Marshall and Davis stated that in normal animals drinking water, the excretion is directly proportional to the concentration of urea in the blood; then McLean devised a formula based on the total

amount of urea excreted, the weight of the patient and the urea in the blood. In 1916 Addis and Watanabe concluded that the normal kidney under constant conditions possesses a very constant function, and Addis and Drury later developed their index, which is calculated on the amount of urea in one hour's urine expressed as a ratio of the urea in 100 cc. of blood. In 1921, Austin, Stillman and Van Slyke published their formula,

$$K = \frac{D}{B\sqrt{V\,W}},$$

where D is the urea output expressed in grams per twenty-four hours, B the blood urea, in grams per liter, V the volume of urine in liters per twenty-four hours, W the body weight in kilograms, and K the excretory constant. They found that K has a value of 7.5 to 3 for normal man. In 1924, Stander, Duncan and Moses proposed an index

$$X = \frac{B \times T.N.}{D}$$

where B is the urea-N in milligrams per 100 cc. of blood; $T.N.$ the total N in grams per twenty-four hours of urine, and D the urea N in grams per twenty-four hours of urine. These authors have been unable to obtain uniform results for the urea excretion rate with any of the above formulae, and therefore feel that the urea excretion rate is not of great value in differentiating chronic nephritis from the other types of pregnancy toxemia.

Rabinowitch, on the other hand, places great reliance upon the "urea concentration factor" and regards it as a more sensitive index of kidney function than the other tests generally used. The routine procedure, as described by Mills and Rabinowitch, is as follows:

The patient takes no food nor fluids of any kind after 7.00 p.m. the evening before the test. At 7.00 a.m. the day of the test the patient voids, and the specimen is discarded. The patient is then given 15 grams of urea dissolved in 150 cc. of water flavoured with lemon juice. The blood is collected two hours afterwards, and the urine one and two hours after the ingestion of the urea. The value of the factor is obtained as follows:

$$\text{Factor} = \frac{\text{milligrams urea per 100 cc. blood.}}{\text{milligrams urea per 100 cc. urine (second hour)}}$$

It appears scarcely necessary to reiterate that only by performing the test under the standard set of conditions described can the results be of real clinical value. The average normal value was found to be 40.

Since then an attempt has been made to measure, quantitatively, the efficiency of the kidneys, at least in so far as the excretion of urea is concerned—by the application of well recognized thermodynamic laws. The 'urea concentration factor' forms an essential part of this procedure. For theoretical purposes, as described, it was necessary to slightly modify the routine and calculation of the factor. This consisted in dividing the concentration of the urine urea, by the arithmetical mean concentration of the blood urea obtained both before and two hours after the ingestion of the urea. Thus:

$$\text{Factor} = \frac{\text{Urine urea concentration (second hour)}}{\frac{\text{Blood urea concentration before} + \text{blood urea after.}}{2}}$$

This increases the value of the factor from 40 to 50 for normal individuals."

Patch and Rabinowitch state that

"in lesions of the kidneys whether primarily or secondarily associated with azotemia or other evidence of impairment of the excretion of nitrogenous substances, the determination of the urea concentration factor is of greater value for diagnosis and a better index of progress than the individual consideration of either the blood urea nitrogen or urine urea concentration."

Clauser has modified the renal function test of Nyiri as follows: The bladder is emptied and the urine saved as a control. Ten cubic centimeters of 10 per cent sodium hyposulphite are injected intravenously and specimens obtained from the bladder in one, two, and three-hour periods. Twenty cubic centimeters of the urine are shaken up with half a gram of animal charcoal for two or three minutes and then filtered. To 10 cc. of the filtrate is added a little starch and then titration with 1/10 normal iodine solution carried out. The amount of iodine solution used, multiplied by 15.8, gives the amount of substance in 10 cc. of urine that is capable of binding iodine. He concludes that a definite decrease in renal function, which in normal pregnancy is very slight, becomes marked during labor; and that during the puerperium the kidney usually regains its function in less than five days. This test, he claims, is of value in nephritis complicating pregnancy.

Kingsbury and Swanson suggested a new kidney function test which consists in estimating the synthesis and elimination of hippuric acid. The patient is given sodium benzoate, 95 per cent of which is eliminated in the form of hippuric acid within three hours in the normal person. In chronic nephritis, the rate of elimination is the same, which proves that the kidney has little to do with the synthesis of hippuric acid. Their results show that this test varies in the same general direction as the phenolsulphonephthalein test but is capable of revealing abnormal renal conditions to a finer degree. Orlovius places great confidence in the estimation of creatinin and claims that where the clinical symptoms in nephritis during pregnancy are doubtful, the estimation of creatinin will give valuable information as to the prognosis. He uses the test of Neubauer in which creatinin dissolved in glucose is given by mouth, early in the morning, and the urine examined for creatinin at 6 hour intervals.

Harrison and Hewitt indorse the Andrewes Diazo test, although it and urea retention do not run strictly parallel. Bowen states that when the concentration of urea in the urine in the second hour is below 2 per cent, there is evidence of kidney insufficiency. MacKay and MacKay state that a patient with chronic interstitial nephritis may have a blood urea concentration within normal limits, even though only 50 per cent of normal functioning kidney tissue is present. Wittenbeck showed that the increase of uric acid in the blood does not depend on disturbances of kidney function.

Eckelt carried out a large series of tests on the kidney function during pregnancy, and observed no difference in the functional activity of the kidney in non-pregnant and pregnant women. In the so-called "kidney of pregnancy" there was an insufficiency only in the excretion of water and sodium chloride; and it is for this reason that he suggests that in the kidney of pregnancy, milk should not be used in the diet and advises a restriction in sodium chloride.

DeWesselow states that there are two distinct types of defect in renal function, namely, inability to excrete threshold substances, and inability to deal with non-threshold substances. As a typical example of threshold substances he mentions sodium chloride, and as a non-threshold substance urea, and states that defective elimination of sodium chloride is characteristic of hydremic or parenchymatous

nephritis, while in azotemic or interstitial nephritis there is an inability to excrete urea.

From the consideration of these various kidney function tests as well as from personal experience with certain of them in cases of pregnancy complicated with nephritis, it appears to the author that the urea concentration test, as developed by Rabinowitch and his coworkers, will prove the most useful in diagnosis and prognosis. The application of this test in a large series of toxemias may prove very instructive.

Chemical changes. Krauter investigated the hydrogen ion concentration of the urine in order to study the regulatory function of the kidneys on the acid base equilibrium during pregnancy. He concludes that the hydrogen ion concentration is more stable during pregnancy than in the non gravid state. The administration of acid or alkali does not change the acidity of the urine during pregnancy. From this the author concludes that the kidney function must be impaired, being less able to excrete the excessive amount of acid or alkali which may be present in the body. Rosenburg and Hellfors found that in renal insufficiency the acidity of the urine could not be changed by administration of alkali and believe that this is due to a disturbance in the acid base equilibra between tissue and blood. They also studied the urinary ammonia and found that in normal persons the ammonia decreases after the administration of alkali, whereas the opposite effect follows in cases of renal insufficiency. This they explained on the basis that in the person with abnormal kidneys there is a deficiency of alkali, and the administration of alkali results in setting free ammonia that has been used in the tissues for the neutralization of acids. Bloor, in his studies on blood lipoids in nephritis, noted a high fat in the plasma and corpuscles and high lecithin in the corpuscles, the cholesterol values being practically normal. He regards this abnormality as the result of a retarded assimilation of fat in the blood, which in turn is thought to be a manifestation of a general metabolic disturbance, brought about by a lowered alkali reserve of the blood and tissues.

Stander, Duncan and Sisson observed in nephritis only a slightly elevated uric acid but a definite increase in the blood urea nitrogen when expressed as a ratio of the non-protein nitrogen, as well as when ex-

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pressed as a ratio of the urea nitrogen percentage in the urine. The latter ratio $\left(\frac{\text{B.U.N.}}{\text{U.N. per cent}}\right)$ is approximately 16 in normal pregnancy, while it rises to about 24 in nephritic toxemia. These investigators found that the inorganic elements were within normal limits in this type of pregnancy toxemia. De Wesselow in a clinical study of the toxemias of pregnancy noted that a definitely raised urea content of the blood, that is about 40 mgm. per 100 cc. of blood, is proof that the kidney is severely damaged, and affords an indication for interruption of pregnancy. Where there is no increase in blood urea, this author suggests that a urea concentration test be carried out, and, when the result is below 2 per cent, that pregnancy should again be interrupted. Dossena states that a differential diagnosis between nephritis and pregnancy nephropathy (low reserve kidney) can be made on the basis that urea in the blood is always increased in nephritis and never in nephropathy. In nephropathy there is an increase in chlorides and consequently water retention and oedema. Bunker and Mundell found a varying degree of nitrogenous retention in all their cases of nephritic toxemia. In a follow-up study of their cases, they were able to demonstrate a kidney lesion in some cases as late as two years after delivery.

Jackson, Sherwood and Moore attempted to corroborate the polypeptide nitrogen findings of Hulse and Straus, who had observed values as high as 30 mgm. per 100 cc. of blood in cases of hypertension. Hulse as well as Blau, gave the normal blood plasma polypeptide nitrogen as 3 mgm. per 100 cc. of blood. Jackson, Sherwood and Moore found the normal peptide nitrogen to range between 0 and 5.7 mgm., with an average of 0.8 mgm. In their cases of hypertension the peptide nitrogen ranges between 0.0 and 5.2 mgm., with an average of 0.7 mgm. They conclude that there is no direct evidence to show that in hypertension the peptide nitrogen rises sufficiently to be of prognostic significance.

Myers and Short studied 7 cases of nephritis with marked nitrogen retention and noted that there was no increase in the potassium content of the serum or of the whole blood, and believed that their observations do not lend support to the suggestion of Smillie that some of the symptoms of uremia may be due to a potassium poisoning. Denis and Hobson conducted a study on the inorganic constituents of

blood serum in nephritis and found a marked increase in the sodium chloride in 18 per cent of their cases; the inorganic phosphate fraction was increased in 45 per cent of the cases. They believe that sodium and chlorine are excreted with great ease even where the kidneys are badly damaged. Underhill and Wakeman produced severe nephritis in rabbits by sublethal doses of sodium tartrate, and noted a marked decrease in the chloride concentration of the blood and a corresponding increase in relative blood volume. With recovery the chloride concentration becomes normal.

In general, it may be said that in severe nephritis complicating pregnancy an elevated non-protein nitrogen, urea nitrogen and often a slight increase in uric acid will be found in the blood stream, but the absence of these abnormal findings does not exclude nephritis. The sodium chloride content of the blood, a renal function test, the patient's blood pressure, the amount of albumin in her urine, her past history, and the duration of pregnancy may all contribute in establishing the diagnosis.

Eye changes. The opthalmoscopic study of the eye grounds often aids in differentiating nephritic toxemia from other types of pregnancy toxemia. Albuminuric retinitis is sometimes seen in nephritis complicating pregnancy, while, according to Miller, it is never present in true eclampsia or pre-eclampsia. Wolff and Zade, in a clinical study of cases with marked renal disturbances, found that the definite forms of kidney disease in pregnancy could not be differentiated clinically, and state that albuminuric retinitis may be associated with ordinary "kidney of pregnancy" in the presence of a chronic nephritis.

Kollert states that hypertension and narrowing of vessels appear to be the essential factors in the origin of nephritic retinitis. With a falling blood pressure, healing may ensue. Deposits of cholesterol esters in the eye frequently occur with hypercholesteremia, but only when retinal disease is already present. Couvelaire reports two cases of retinitis without increase of the blood nitrogen, the retinitis occurring at about the fifth month of pregnancy. Complete blindness, albuminuria, and high blood pressure, were present in both cases, and each made a complete recovery after delivery of a six and a half and five months' foetus, respectively.

Rochet does not regard albuminuric retinitis as an absolutely un-

favorable diagnostic sign in nephritis. Fink states that in cases of acute blindness or severe amblyopia with normal eye grounds, the removal of the foetus becomes necessary only if uremia is present. On the other hand, visual disturbances of gradual onset are extremely serious. He furthermore believes that the theory of retinitis gravidarum occurring only with chronic nephritis is incorrect, and that this condition is often associated with a "kidney of pregnancy" and eclampsia. He does not agree with Schoeitz that patients with chronic nephritis and eye ground changes should be sterilized.

Capillaries. Following the fundamental work of Krogh on capillaries, some remarkable changes have been observed in the capillary walls in cases of nephritic toxemia. Nevermann, Hinselmann, Linzenmeier, Heynemann, and Niekan describe varying degrees of capillary stasis with changes in the size of the arterioles. Spasm of the walls of these small vessels has been noted and is supposed to be due to a toxic stimulation of the nervous supply or of the musculature of the vessel-walls. This capillary spasm, which can be observed in the nail-fold vessels, results in dilatation of other portions of the vessels, causing stagnation of the blood flow with resultant anoxemia. Mufson has studied the capillaries in a series of toxemias with hypertension at the Sloane Maternity Hospital, but found no consistently typical picture. He regards the presence of a high capillary pressure in these "hypertensive toxemias" as indicating an unfavorable prognosis for mother and child.

In normal pregnancy, Baer and Reis could find no abnormality in the capillary loops, neither as to morphology nor blood flow, but they observed elongation of the loops and increased tortuosity in cases of nephritis complicating pregnancy. In the latter condition the character of the capillary flow also showed abnormal deviations, so that the authors regard capillary microscopy as of value in differentiating true nephritis complicating pregnancy from the other toxemic conditions.

Kylin views nephritis occurring during pregnancy as practically identical with acute glomerulonephritis. In both conditions, he writes, the changes in the capillaries are identical, and the capillary pressure is raised. The modern tendency seems to be to regard nephritis as a systemic disease, rather than one strictly limited to the kidneys.

Prognosis. In this clinic during the past four years the immediate maternal mortality in nephritis complicating pregnancy has been 3.3 per cent, but it is evident that this figure does not give us a true concept of the severity of the disease. Every year we see women who had been discharged from the hospital a year or two previously, at the end of a fairly normal puerperium, succumb to chronic nephritis. We have no accurate method of determining the amount of damage to the kidneys done by the pregnancy. Jaschke, in discussing the prognosis of kidney disease in association with cardiac disease considers the condition very serious, and contends that labor should be induced as early as possible. It is only by reducing the work of the kidneys and the heart that the patient can be given any chance for the future. Hussey regards nephritis as a very serious complication of pregnancy, and is convinced that the gestation itself exerts an injurious influence on an already existing nephritis.

Very occasionally one may have to deal with cortical necrosis of the kidney, or with a nephrectomy preceding pregnancy. Manley and Kleinen reviewed the literature on cortical necrosis of the kidney in pregnancy, and found only 20 cases in all. Most of these were in the latter half of pregnancy, and usually associated with premature labor, and with stillborn babies. They reported the case of an eighth month pregnancy in a primipara, in whom the onset of the disease was very sudden. The case was complicated by severe hemorrhage and caesarean section was performed. There was total anuria for twelve days and the patient came to autopsy, where the characteristic lesions of cortical necrosis were seen. Rolleston also reports a case of symmetrical necrosis of the cortex of the kidney directly following childbirth. The symptoms in this patient resembled those of obstructive anuria. Necrosis of the cortex is probably intimately connected with thrombosis of the interlobular renal vessels.

Jardin and Kennedy studied 12 cases in which the suppression of the urine occurred as a complication of pregnancy. They found symmetrical necrosis of the renal cortex in 6 cases; in three of them there was evidence of pre-existing chronic inflammation, while in the other three the condition was cortical necrosis. But cortical necrosis of the kidney in pregnancy is so rare a condition that it need hardly be considered under the nephritic complications of pregnancy.

Matthews analyzed a large series of cases of nephrectomy and preg-

nancy and came to the same conclusions as Schmidt, who states that a woman with one healthy kidney does not run much greater risk, nor does the foetus, than the woman who has two healthy kidneys. Also Borelius states that normal pregnancy can follow nephrectomy without any difficulty, provided the remaining kidney is normal. Buschmann reports three cases of unilateral impairment of the kidney during pregnancy and suggests that pressure from the gravid uterus affecting the right kidney more than the left may play a part in the production of this impairment. He considers that the diminished renal function is due to primary venous stasis, just as one sees in advanced heart disease, as well as to direct pressure of the uterus upon the kidneys.

Treatment. From a consideration of the prognosis in nephritis complicating pregnancy, as outlined above, it will be clear that one assumes a grave responsibility by allowing gestation to proceed in the face of an underlying nephritis. Stander writes

"If the nephritic condition is severe, immediate termination of pregnancy becomes imperative. In the milder types of chronic nephritis rest in bed and dietetic treatment occasionally enable us to carry the patient to term without any serious harm to the mother, but it is well to remember that such an outcome is the exception rather than the rule. Furthermore, how can we be sure that the underlying renal condition has not been aggravated by the strain of the latter months of pregnancy, and that the patient's life has thereby been shortened, although this increased damage to the kidneys may not be apparent at the time of delivery? I strongly advocate the termination of pregnancy in all cases complicated by an underlying chronic nephritis, unless marked and rapid improvement follows the conservative treatment of rest in bed with restricted low-protein (and in some instances salt-free) diet and plenty of fluid. The patient's past history, both medical and obstetrical, the duration of the present pregnancy and the subjective and objective findings, enable us to form an opinion as to the severity of the nephritic condition."

Smith believes that a diet of lower protein content than is usually employed in the treatment of chronic nephritis, may be used in cases with nitrogenous retention. He bases the amount of protein allowed in the diet on the amount of non-protein nitrogen which the patient is able to excrete in twenty-four hours. The amount of protein nitrogen in the diet should be less than the total amount of non-protein nitrogen in the urine in twenty-four hours. Peters, on the other

hand, argues that in patients with albuminuria, the loss of protein must be indirectly compensated for by increasing the protein in the diet, otherwise a drain on tissue protein will follow. This is contrary to the usually accepted views that high-protein diet leads to kidney damage.

In nephritis complicating pregnancy the low-protein diet seems to give the best results as far as the dietary treatment is concerned. Where there is marked oedema, salt in the diet is contraindicated. As stated above, pregnancy should be terminated whenever there is no improvement on the strictly medical treatment and evidence of progressive renal damage is apparent. Too often the mother is subjected to further kidney injury, which may soon prove fatal, in order to obtain a living child; whereas the life of the mother should be our first consideration. Our attitude in this clinic has become more radical during the past five years, and if prompt improvement does not occur under conservative medical treatment, we terminate pregnancy by means of a bougie or bag and upon discharge from the hospital the patient is advised as to the use of contraceptives. Often it is advisable to terminate the pregnancy by caesarean section and effect sterilization at the same time especially where contraceptive advice will probably be ineffectual.

IV. Pre-eclampsia

The term "pre-eclamptic toxemia" has caused a great deal of confusion, as some writers have used it when referring to any one of the late toxemias of pregnancy. The author has advocated the discontinuance of this term and has suggested instead the word "pre-eclampsia," and furthermore that its use be limited to the relatively small group of cases in which the patient presents the signs, symptoms and laboratory findings of eclampsia but has not yet developed convulsions. In other words, pre-eclampsia is essentially eclampsia before the outbreak of convulsions and coma. Bar suggested that we designate eclampsia without convulsions as "eclampsism," which is undoubtedly synonymous with severe pre-eclampsia. When used in this restricted sense, pre-eclampsia is relatively rare, not exceeding five per cent of all the toxemias of the latter half of gestation, and occurring about fourteen times in every thousand deliveries, according to the figures of this clinic.

Pre-eclamptic patients usually show the same picture as eclampsia, except that convulsions are absent. The patient is acutely ill with a great amount of albumin and some casts in the urine and a high blood pressure. After delivery there is a prompt return to the normal blood pressure level and the urine soon becomes albumin free. The author believes that pre-eclampsia is a manifestation of the same disease entity as eclampsia, and differs from it only in so far as convulsions and coma do not occur. In other words, the pre-eclamptic patient has a potential eclampsia, being, as the name implies, in the stage preceding eclampsia. The disease develops usually during the last two months of gestation and its onset may be quite abrupt, as is so often the case in eclampsia. The first danger signal, especially where there has been no prenatal care, is frequently a complaint of sharp epigastric pain or failing vision. Within a short time the blood pressure has climbed to a high level, usually around 190 systolic and 110 diastolic. The urine contains three or more grams of albumin per liter, and there may be marked oedema of the face and extremities. Analysis of the blood reveals an elevated and steadily increasing uric acid content, and often a lowered CO_2-combining power. As a rule there is no nitrogenous retention, both the non-protein nitrogen and urea nitrogen being within normal limits. The blood sugar, the inorganic elements, calcium, magnesium, sodium, potassium and phosphorus in the blood, as well as the nitrogen partition in the urine, are usually within normal limits. Examination of the eye-grounds may show oedema of the retina, retinal hemorrhages or even detachment of the retina, but no albuminuric retinitis. If death does not occur during the attack delivery of the child is promptly followed by the disappearance of all abnormal findings within a week or two.

Mills states that the symptoms of headache, nausea and vomiting, epigastric pain and colonic distress are to be regarded as indicative of pre-eclampsia. According to this author the eyes are involved in about 90 per cent of all cases as a result of a physiologic enlargement of the pituitary gland. Different degrees of contraction of the visual fields by pressure upon the optic commissure and tracts are the result of this enlargement. He believes that the symptoms of pre-eclampsia arise from local intracranial pressure of the enlarged hypophysis as well as from increased function of this gland. He advocates that we separate the pre-eclamptic symptoms into those of pituitary origin and

those coming from a true toxemia of pregnancy, and that this can be done by a systematic examination of the visual fields and eye grounds. Dice finds that the first objective signs in the eyes of pre-eclamptic patients are a haziness of the fine detail of the fundus, a beginning retinitis; and he empties the uterus when this stage is present.

Klaften observed that the depth of respiration in pre-eclampsia is many times greater than in normal individuals, and he regards a rapid increase in the respiratory depth as a sign of an aggravation of the toxemia and as a warning of impending eclampsia. He also thinks the persistence of deep breathing after a convulsion is a very unfavorable sign.

Cary in discussing the etiology of pre-eclampsia states that a toxic substance or substances are elaborated which give rise to the syndrome of eclampsia and that this toxic substance is probably an early split product of the protein molecule. The source of the toxin is not single, and it may enter the maternal circulation in one of three or more ways, from autolysis of degenerating placenta, absorption into the large intestine of split products of bacterial origin, and from primary foci of infection. He was able, by extracting with normal salt solution placental tissues free from blood, to obtain a substance toxic to guinea pigs, when administered intraperitoneally. He could destroy the toxicity of this substance by incubating it with pregnant horse serum. He believes that these factors are suggestive that a substance is elaborated in the autolysis of the placenta which can produce eclamptic-like symptoms in experimental animals. This author has developed a method of treatment of pre-eclampsia, which consists in rest, increased elimination, and a salt-free, protein-free diet. Carbohydrates are given freely as well as buttermilk in order to change the intestinal flora from a putrefactive to a fermentative type. Sodium bicarbonate and in some cases calcium salts are administered in order to increase the urinary output and to decrease the irritability of the nervous system. Curl also believes in a low-protein diet in the treatment of pre-eclampsia.

The treatment of this type of toxemia varies greatly with different authors, depending on their views regarding the treatment of true eclampsia. Harding and Van Wyck are of the opinion that protein and fat produce no ill effects in the treatment of pre-eclampsia, but that salt in the diet is of main importance, as it always aggravates the

symptoms. The restriction of salt in the diet should not be continued for too long a period, and they determine the amount of salt in the diet by collecting twenty-four hour specimens of urine and finding the point at which the salt excretion reaches a constant minimum of 2 or 3 grams. They recommend the total restriction of salts one week in every four in addition to the usual prenatal care. Bland and Bernstein also advocate a salt-free diet in the treatment of this type of toxemia and report 13 cases successfully treated.

Mayer has treated 24 patients suffering from pre-eclampsia with ultra violet rays. The effect of this treatment is to lower the blood pressure and to decrease the amount of albumin in the urine. The rays are given from three to ten minutes at a time at a distance of 75 cm., and the treatment repeated. Only one of his patients developed eclampsia.

Peterson also regards pre-eclampsia as a type of intoxication which will end in convulsions, unless properly treated. He states that when, in spite of treatment, the albuminuria, cylindruria and blood urea increase along with a rise in blood pressure, and oedema, headache and eye disturbances become more marked, the uterus should be emptied. This author is an advocate of caesarean section but admits that each case must be judged by itself, taking into account the severity of the intoxication, the condition of the birth canal, and the size and condition of the child. Poucher is another advocate of caesarean section in pre-eclampsia.

From the work of Davis, Stander and others on anesthesia it seems advisable to the author that caesarean section under spinal or local anesthesia should be our method of choice in certain cases of pre-eclampsia, where the outbreak of an impending eclampsia appears imminent. Often the cervix is tightly closed, especially in primiparae so that the introduction of a bougie or bag with a long drawn out labor may do far more harm than a caesarean section performed quickly and without the use of a general anesthesia. If the pre-eclamptic patient does not improve promptly with rest in bed, restricted diet and sedatives, such as morphia and chloral hydrate, and we fear the development of true eclampsia, the patient should be delivered as promptly as is consistent with safety to the mother, and often a caesarean section under local or spinal anesthesia will give the best results in this type of case.

As the author regards pre-eclampsia simply as a stage in the develop-

ment of eclampsia, further discussion of its etiology will be given in the section on eclampsia. Likewise additional details regarding its treatment will be incorporated in the same section.

V. Eclampsia

"Eclampsia" is derived from the Greek ἔκλαμψις, meaning a shining forth or flash, and was first used by Hippocrates to denote a fever of sudden onset, and later by Sauvage. At the end of the eighteenth century, the German writer, Gehler employed the word "eklampsie," and gradually it came to mean a definite disease entity occurring during pregnancy. As used today, the term signifies an acute toxemia during the latter half of pregnancy or early puerperium, which is usually associated with clonic and tonic convulsions, followed by varying degrees of coma. It is perhaps more correct to define eclampsia as a symptom-complex, resulting from pregnancy, with cerebral phenomena as the most outstanding characteristic. Generally we regard eclampsia as synonymous with convulsions occurring during pregnancy, although eclampsia without convulsions is a recognized entity, sometimes corroborated in the postmortem room. Again, convulsions of epileptic, hysterical or meningeal origin, as well as those associated with uremia or acute yellow atrophy may occur during gestation, so that the appearance of fits does not necessarily mean the pregnant woman is suffering from eclampsia.

In the literature of the eighteenth century we find excellent descriptions of convulsions occurring during pregnancy or labor. Amberg, in 1713, described generalized convulsions in a pregnant woman, who was cured after the use of nervous powders and phlebotomy; undoubtedly an example of what we now know as intercurrent eclampsia. Many of the text-books on midwifery of the latter part of the eighteenth and early half of the nineteenth centuries contain detailed accounts of convulsions, or "epileptic fits" incident to child bearing, and ascribe them to various causes, such as uterine irritability, movements of the foetus, sudden emotions of the mind, excessive flooding or a blood plethora, and epilepsy. Alexander Hamilton in his "Elements of the Practice of Midwifery," published in 1775, writes

"1. Convulsions at an early period of Pregnancy chiefly happen to young Women of a plethoric sanguine habit, and can therefore only be removed or

palliated by a free and bold use of the Lancet, by an open belly, cool regimen, and spare diet. After plentiful evacuations, if the stomach be loaded with acrid Saburra or putrid Bile, a gentle Puke may be of use: But such remedies, on these occasions, must be employed with great caution. Instead of a Plethoric, if the Patient is of a nervous habit, a very necessary and important distinction, the intentions of cure will essentially vary. For here Opiates in large doses and frequently repeated, emollient clysters, stupes applied to the legs, the Semicupium, and every other means to soothe the nerves, and remove Spasmodic stricture, will prove the most effectual remedies. If insensible or comatous, Opium, Musk, and other Antispasmodics should be exhibited by way of clyster, and the Patient ought to be roused by Epispastic and stimulating Cataplasms applied to the legs and hams. Convulsions succeeding profuse evacuations, are generally mortal. The Vis Vitae, in such circumstances, must be supported, by replenishing the vessels with the utmost speed: This is to be done by pouring in nourishing fluids as fast as possible by the mouth, and by clyster; warm applications should also be made to the stomach and feet, and nervous cordials given internally along with Opium.

The treatment of Epileptic Fits, depending on other causes than those now mentioned, must be regulated by a proper attention to the particular symptoms with which they are attended.

2. In the advanced months, such Complaints are more to be dreaded than in early gestation, as they generally proceed from the irritation occasioned by the distention of the Uterine Fibres, or by the pressure of the Uterus on the contiguous Viscera: Hence the natural functions of these parts will be interrupted, the circulation of their fluids will be impeded, and the Blood, being thus prevented from descending to the inferior parts, will be derived in greater proportion to the Brain, and overcharge that Organ.

The Cure must, in this case, chiefly rest on copious and repeated Bleedings, an open Belly, and spare Diet.

3. Lastly, When Fits come on with Labour-pains, a speedy Delivery, if it can be done with safety, either by turning the Child, or by extracting with the Forceps when the Head is within reach, will prove the most effectual Cure."

Incidence. From a very careful study of all statistics published up to 1924, Hinselmann concludes that eclampsia occurs once in every 253.7 women entering a lying-in hospital, in other words in 0.39 per cent; while in private practice the frequency is one in 1816.6 or 0.05 per cent. The total incidence of eclampsia, according to this author, is one in every 867 births (0.12 per cent). Although the birth rate in

various countries differs markedly, and in some countries there are no figures as to birth rate, Hinselmann has estimated that with the world's population at 1,702 millions of people and the yearly birth rate at approximately 56 millions, the total number of eclamptic patients is approximately 64,570 per annum. Williams states that eclampsia occurs about once in every 500 labors, while in the lying-in hospitals the incidence is about one in every 130 deliveries or 0.75 per cent.

Zacheral observed 188 cases of eclampsia in 33,700 deliveries in the clinic at Graz, an incidence of 0.57 per cent, while Zweifel reports 190 cases of eclampsia in 29,733 deliveries in the Woman's clinic at Munich (0.64 per cent). The Hamburg Municipal Obstetrical Institute, according to Westphal, had 189 cases of eclampsia in 22,809 deliveries (0.83 per cent). Heinlein found among 14,000 deliveries, 253 cases of eclampsia, a percentage of 1.8; while Hingston and Mudalier also reported a high incidence of eclampsia, namely, 1.73 per cent, in the Government Hospital for Women at Madras, India. Nevermann found that in 385,226 births, eclampsia occurred 559 times, in other words, one in 689.13 births, a figure which corresponds fairly closely with that given by Hinselmann. Leidenius gives the statistics for 1911–1914 at the University Clinic at Helsingfors, and reports the total incidence of eclampsia as 0.6 per cent.

From these figures it appears that eclampsia occurs about once in every 500 to 800 deliveries; while the incidence in the obstetrical clinics is approximately one in every 150 births, because of the proportionally excessive number of seriously ill patients referred to hospitals for treatment.

Weather. Eclampsia varies in frequency at different times of the year and many authors have tried to demonstrate a connection between its incidence and weather conditions.

As early as 1825 Madame Lachapelle wrote that certain authors, Smellie among them, attributed a certain influence to the atmospheric conditions on the production of eclampsia. Schräder in 1882 and Olshausen in 1890 stated that eclampsia varied with the seasons. The latter observed 88 cases of eclampsia in the period of March to August and 105 cases from September to February. Glockner observed the greatest incidence from October to February. Knapp also observed the greatest incidence in the winter months. Schreiber, on the contrary, states that the greatest number of eclamptics occurs in the

months of July and August and the smallest number in November and February.

Croom from the statistics of the Edinburgh Maternity Hospital concluded that a sudden alteration in the temperature and rainfall, irrespective of any particular season, may affect the frequency of eclampsia. Hammerschlag in 1904 investigated the period 1898–1902 in East Prussia and could find no association between weather and eclampsia; while Linzenmeier found that eclampsia was especially frequent in the fall and in the spring and particularly on days with a sudden drop in temperature and northwest winds. v. Heuss made a very detailed study for the period 1908–1922 in Berlin and concludes that there are more cases of eclampsia on cold than on warm days, and that cold weather, fog and lowering temperatures are especially conducive to it. Hoenhorst, on the other hand, although he states that the incidence of eclampsia may possibly be enhanced by the effect of unfavorable weather on the excretory functions of the body leading to retention of toxins in the body, concludes that the weather is not a factor in the cause of the toxemia, but it may promote the onset of convulsions. Jacobs also states that eclampsia follows cold weather. Ragusa studied the incidence of eclampsia in Rome for a period of ten years but could find no connection between it and the weather.

Harrar, studying a series of cases of eclampsia at the New York Lying-In Hospital, found that the frequency of the disease was at its highest during the month of April, and that unsettled, damp and cold weather, as usually occurs in the spring months, is accompanied by an increase in the number of eclamptic patients.

There have also been studies to show that eclampsia is more frequent in large cities than in the country. v. Heuss thinks that the former tend to produce hypertension and so eclampsia, and consequently that it is primarily a disease of large cities. He found that in Germany 73 per cent of the fatal cases occurred in women of the industrial classes living in the large cities, as against 12 per cent living in the country, and attributes this variation to differences in diet and hygiene.

There also seem to be regional variations in the frequency of eclampsia. Ryan as early as 1831 stated that eclampsia is more frequent in England than in France. Madame Lachapelle found eclampsia to occur once in 567 in France, whereas in England according to the figures of Merriman, the incidence was one in 42. It is well known that

eclampsia is very common in Glasgow and its surrounding country. Hinselmann writes that in Germany, with a population of 60 million, there are about 2484 cases of eclampsia every year, while Eden reports the total incidence in Great Britain as 2800 among a population of only about 40 millions.

Influence of war. One of the interesting by-products of the World War, was the observation that the incidence of eclampsia was greatly reduced in the countries affected by the so-called hunger blockade, and gradually returned to the usual figure after the blockade wa lifted. Thus Ruge reports that in the University clinic in Berlin there were 15 cases of eclampsia in 1916 as compared with 45 cases i the year preceding the war. Mayer, Warnekros, Schülein, v. Jaschke Zangemeister, Davidson and Miller, all report a lower incidence o eclampsia during this period. The figures of Warnekros are ver indicative and are given in detail.

YEAR	BIRTHS	ECLAMPSIA	PER CENT
Universitäts-Frauenklinik, Berlin			
1910	1,476	62	4.2
1911	1,775	56	3.1
1912	1,868	59	3.2
1913	2,004	52	2.6
1914	1,994	51	2.6
1915	1,794	32	1.8
1916	1,430	12	0.8
Charité			
1912	3,320	78	2.4
1913	3,570	84	2.4
1914	3,350	66	2.0
1915	2,518	36	1.4
1916	1,400	8	0.57
Rud. Virchow-Krankenhaus, Wöchenerinnenheim am Urban, Wöchenerinnenheim Norden			
1912	2,942	57	2.0
1913	3,464	42	1.2
1914	3,496	40	1.2
1915	3,511	42	1.2
1916	2,462	25	1.0

Zangemeister made a very detailed study of this question and found that for the period January 1, 1911 to June 30, 1915, the incidence of eclampsia was 1 in 70, whereas during the period of July, 1915 to December, 1916, it decreased to 1 in 104. (These figures are based on the statistics of the various German clinics.) Hinselmann, on totaling all cases from lying-in hospitals reported in the literature, concludes that the incidence before the war was 1 in 69.5; during the war 1 in 118.4; and after the war 1 in 78.6. Furthermore, the total incidence of eclampsia throughout the country also showed a marked decrease during the war. The statistics for Baden indicate that the frequency before the war was 1 in 595; during the war, 1 in 961, and after the war 1 in 631.

Sachew also investigated the incidence of eclampsia by months during the years of the World War, and observed that it decreased greatly during the last years of the war, when the diet consisted mainly of carbohydrates. This author is of the opinion that meteorlogical conditions also had some effect on its frequency, because the wet months produced more cases, probably because of interference with the excretory functions of the skin. In Sweden, during 1917–1918, when there was a control of food supplies, Groene found a distinct decrease in the frequency of eclampsia. On the other hand, Bublitschenko, observing the cases of eclampsia for a period of ten years ending 1922, in Petrograd, Russia, noted that the incidence increased during the war, contrary to the findings in Germany, France and England, and this notwithstanding the revolution and long period of famine. His observations speak against the theory that the decrease in protein and fat, and the increase in carbohydrates in the diet was responsible for the diminished incidence.

Various reasons have been advanced to explain this lowered incidence during the World War, and the one most generally given is the change in character of the diet incident to the war. The women undoubtedly received a relatively low percentage of protein and fat, with a corresponding increase in carbohydrates, in contrast to the soldiers who were well fed.

But there were other factors, such as inefficient conveyance, and the crowded conditions of the hospitals, that may explain the lowered incidence of eclampsia during the years of the war. We know that

eclampsia is approximately many times more frequent among primiparae than multiparae, and it is possible that a change in the ratio of primiparae to multiparae might have taken place during the war. Hinselmann gives the figures for Baden, showing that such a change did not take place during the war.

Period 1905–1914 $\frac{\text{Primiparae}}{\text{Multiparae}} = \frac{14390}{51140}$, (Primiparae = 22 per cent).

Period 1915–1918 $\frac{\text{Primiparae}}{\text{Multiparae}} = \frac{7605}{26947}$, (Primiparae = 22 per cent).

Period 1919–1920 $\frac{\text{Primiparae}}{\text{Multiparae}} = \frac{18728}{35427}$, (Primiparae = 53 per cent).

From these figures it is evident that there was no greater relative decrease in primiparae than in multiparae during the war, and consequently the decline in eclampsia cannot be explained by a change in that ratio. Hinselmann's statistics for the post-war period are exceedingly interesting, and indicate that the marked increase in primiparae, from 22 per cent in 1915–1918 to 53 per cent in 1919–1920, should have resulted in a much greater occurrence of eclampsia than was actually observed. He reasons that the same factors which were responsible for the decline of eclampsia during the war, may still have been operating in the years immediately following it. The incidence of eclampsia in the post-war period is about the same as in the pre-war period, undoubtedly the result of two neutralizing factors, the great predominance of primiparae over multiparae tending to augment greatly the number of eclamptics, and the "war factor," in which diet perhaps played some rôle, tending to decrease the frequency of the disease.

In the clinic at Bonn, there was a slight relative increase in the number of primiparae during the war, and a still further increase in the years following the war. Also in the State of Hamburg, Hinselmann found an increase in the $\frac{\text{primiparae}}{\text{multiparae}}$ for the years following the war, as during 1917–1918 primiparae made up 34 per cent of the total deliveries, while for 1919 to 1922 this percentage increased to 50.

Parity. As early as 1768 Denman observed that there was a differ-

ence in the incidence of eclampsia among primiparae and multiparae. Velpeau in his text-book, published in 1835, states that eclampsia is more common among primiparae, and quotes Merriman as reporting 36 cases of eclampsia in primiparae, as against 12 among multiparae. All writers on midwifery from that time on have recognized this fact; and recently Zangemeister, in studying a large series of deliveries found 442 cases of eclampsia in 92,122 primiparae, as compared with 180 among 291,718 multiparae, an incidence of 1 in 209, and 1 in 1621 respectively. Hinselmann, likewise, has aggregated the figures of Lantos, Knapp, Bidder and Spitzbarth and estimates the frequency of eclampsia at 1 in 68 primiparae and 1 in 400 multiparae. Although the figures of the latter author show a generally higher incidence, the ratio of primiparae to multiparae is approximately the same as given by Zangemeister.

Types. Eclampsia may occur during pregnancy, labor or the puerperium. If it occurs before the patient has reached term, is followed by recovery, with normal labor subsequently, it is called intercurrent eclampsia, a term introduced by Lichtenstein. If the patient is not in labor, we designate it antepartum eclampsia; if it supervenes during labor, intrapartum eclampsia, and if during the puerperium, postpartum eclampsia. The relative incidence among these three types, antepartum, intrapartum, and postpartum varies greatly, and it is generally stated that the antepartum and intrapartum types are the most frequent. Schröder in 1882 stated that antepartum eclampsia formed 19.6 per cent of all cases. Schaute gave 13.5 per cent for antepartum, 59.8 per cent intrapartum and 26.7 per cent postpartum. Olshausen found 30 per cent antepartum; 56 per cent intrapartum and 14 per cent postpartum. Williams, on the other hand, gives the greatest frequency for antepartum eclampsia, and Eden holds similar views. The former gives an incidence of 55, 22 and 23 per cent for the three types respectively, and the latter, 61.5; 19.2 and 19.3 per cent. Hinselmann, in summing up the figures from all available sources, found antepartum eclampsia in 26 per cent, intrapartum in 53 per cent, and postpartum eclampsia in 21 per cent. Williams comments on this discrepancy, and states that most writers fail to remember that eclampsia usually appears before the estimated date of delivery and that uterine contractions frequently set in with

the first convulsion; in other words, he contends the eclamptic seizure may produce labor, and although the patient is in labor when first seen, the eclampsia had actually antedated the labor and is therefore of the antepartum variety. This appears to be a valid argument, and we are probably safe in concluding that about one-half of all cases of eclampsia are of the antepartum type, and that the other two forms, intrapartum and postpartum, are approximately of equal frequency.

Multiple pregnancies are viewed as predisposing factors in the outbreak of eclampsia. As early as 1824, Miquel-Cerutti regarded hydramnios, monstrosities and multiple pregnancies as causative factors in the development of eclampsia. Williams writes "twin pregnancy and hydramnios appear to act as predisposing factors in the development of eclampsia." Zangemeister states that while in normal individuals, multiple pregnancy occurs once in 79 births, in eclamptic patients it occurs once in 15 births; in other words, five times more frequently than in normal pregnancy. Likewise, Hinselmann, in a comprehensive series of 7645 cases of eclampsia, found that multiple pregnancy occurred once in every 15.7 cases; in other words, an incidence of 6 per cent. Bumm states that multiple pregnancy and hydatidiform mole predispose to eclampsia, but hydramnios does not.

Age and mode of living. Studies have been made to attempt to ascertain the relationship between the occurrence of eclampsia and the age of the patient. Shröder, in 1882, wrote that there is no age limit for eclampsia. A summary of the figures of Buttner, Bidder, Hammerschlag and Spitzbarth, shows that 90.2 per cent of all cases of eclampsia occur between the ages of 14 and 30, and 9.8 per cent after 30 years. Schauta observed that most of his eclamptics occurred before 30 years of age, and that the age of predilection is between 21 and 25 years of age.

We have already noted that eclampsia occurs about 8 times more frequently among primiparae than multiparae, and when it is borne in mind that the majority of first pregnancies fall between the ages of nineteen and twenty-four years, we can readily see why the incidence of eclampsia is so very high at that period.

There is some difference of opinion as to whether the mode of living has anything to do with the incidence of eclampsia. The older authors were of the opinion that it occurred less frequently among the poor

people than the well-to-do. Bard, in 1815, wrote that women "in the higher spheres of life, who have been delicately bred and who indulge themselves in a dissipated and luxurious life, are much more liable to these dreaded and fatal diseases than the hardy inhabitants of the country." We agree with him that eclampsia is more frequent in the large cities than in the country.

Gehler in 1798 said that eclampsia is particularly common among the delicate city women who have a disposition towards this disease, acquired by heritage or as a result of their sedentary mode of living, avoiding every act they are not accustomed to; and that the disease is rare among the country classes. Velpeau and Bluff, in 1834, expressed similar views.

In our own times, Hammerschlag found eclampsia more frequent in the cities than in the country and estimates that there is only one eclamptic for every 1800 births in the latter as compared with 1 in 286 in the former.

Gessner has called attention to the fact that during the war, women did more work than before the war, and that better nutrition fostered by a more active life may have been a factor in the lowered incidence of the disease during the war.

Erroneous conclusions may easily be drawn as to the effect city-life, country-life, or the mode of living may have on the incidence of eclampsia, because of factors that do not lend themselves to ready investigation. Many patients are referred from the country to the city doctor for delivery; record of disease or cause of death is often incomplete in deliveries outside the hospitals, and the exact manner of living of the patient is often not known. Nevertheless, Kosmak is probably fully justified in saying that "eclampsia is as prevalent among the poor as among the well-to-do. It is probably even more prevalent among the poor, unless proper supervision is maintained," and our experience is that in Baltimore it occurs most frequently among ignorant negroes who are too unintelligent to take advantage of the opportunities for efficient prenatal care.

Recurrence. Eclampsia may recur in subsequent pregnancies, although the disease undoubtedly confers a relative immunity. Denman in 1768 noted that eclampsia recurred in certain women. Bumm, in the last edition of his text-book, wrote that about ten per cent of

eclamptic patients have a second attack in a subsequent pregnancy. He differentiates between "widerholte Eklampsie" and "rezidivierende Eklampsie," the former denoting the occurrence of eclampsia in the same individual in a subsequent pregnancy, while the latter means repeated attacks of eclampsia during the course of a single pregnancy.

Williams writes "In my experience, a woman who has had eclampsia is less disposed to the disease in future pregnancies, than one who has never had it."

Hinselmann collected all available statistics on this question, and came to the conclusion that there is a recurrence in only 1.92 per cent, or, to express it another way, he states that in 10,000 cases of eclampsia recurrence in subsequent pregnancies will be noted in 192.

Early and late eclampsia. Although eclampsia usually occurs during the latter third of pregnancy, the disease has been observed in the first half of pregnancy. Ebeler, in 1911, collected from the literature on eclampsia, 55 cases which had occurred during the first half of pregnancy, and Bourne reported a case at the twenty-fourth week of pregnancy. Füth in 1928, reviewed the cases of early eclampsia already recorded, and reports a case of his own at the fourth month, which at autopsy showed typical eclamptic liver lesions and glomerulonephritis. His patient was twenty-two years old, and in the fourth month of her first pregnancy she developed two convulsions. A dead foetus was removed, and the convulsions recurred. The patient died five and three quarter hours after the first eclamptic convulsion. At autopsy it was found that there were no gross lesions in the brain, and only slight changes in the liver and kidneys. Füth believes this to be a case of true eclampsia.

In a personal communication, E. D. Plass described a case of eclampsia in the early half of pregnancy. The patient, aged sixteen, white, was admitted to the hospital after having had 17 convulsions and having been semi-comatose between attacks. The convulsions were preceded by epigastric pain and vomiting. She was treated conservatively along the lines proposed by Stroganoff, and improvement followed. A macerated fetus was passed seven days following the last convulsion. Plass sums up the patient's history as follows: "It would seem that a diagnosis of eclampsia is justified on this patient. The history of convulsions is clear, the patient was admitted in coma,

there was albumin in the urine, and the fetus apparently died at the time of the attacks. The absence of oedema, the normal blood pressure and the fact that there were no convulsive attacks after admission do not seem to me to overweigh the other positive facts. It is regrettable that the patient did not remain in the hospital for further kidney function tests."

Eclampsia has also been reported as occurring weeks and even months following delivery. To my mind it is extremely doubtful whether convulsions appearing four days or more after parturition can be considered due to postpartum eclampsia, and hysteria, epilepsy or meningitis usually will be found to be the underlying cause in such cases. Most, if not all, cases of postpartum eclampsia occur within the first two days following labor.

Constitution. For many years it has been thought that constitutional factors may predispose toward the development of eclampsia. Early references to this may be found in the work of Bluff, Naegele, Späth, Höhl and Scanzoni. In 1891 Schröder wrote: "Es schützt kein Alter und kein Stand vor der Eklampsie. Schlechte Ernährung und Anämie geben keine Disposition dazu, im Gegenteil sind es besonders häufig vollblütige, mit starkem panniculus adiposus versehene Erstgebärende."

Hinselmann states that both delicate (zarte) and strong women may have eclampsia, and that no outward body appearance seems to be a predisposing factor in the development of eclampsia. On the other hand he believes that the structure and function of the different organs of the body, considered as a whole, may give us information as to its incidence, and lays stress on the hemopoietic system, and particularly the vascular volume. Brugsch estimates the heart volume from the transverse diameter of the heart, as measured by the X-Rays. The heart volume is supposed to bear a definite relationship to the trunk volume, and the latter may be estimated by the formula:

$$\frac{\text{Trunk length} \times (\text{chest circumference})^2}{4\,\pi}$$

Normally the heart volume should be from 1/50 to 1/34 of the trunk volume. Although the heart volume may not actually be smaller in eclampsia, Hinselmann believes that the total vascular volume may be

a factor in the production of eclampsia, and has developed a formula to express such a probability. He starts with the equation of Hueppe and Brugsch, which states that the illness equals $f(C.p)$, where f is a constant, C the constitution and p the agent producing the disease. Since pregnancy is the agent responsible for the eclamptic state, eclampsia $= f(C.S.)$, where S represents pregnancy.

Hinselmann further modifies this formula so that finally,

$$\text{Eclampsia} = f\{(S_o \cdot W_f) \cdot Mg_f \cdot a_f \cdot (Mx)_f ?\}$$

where S represents pregnancy; W, labor pains; Mg, vascular system; a, outside circumstances; Mx, possible impaired function of other organs; o, indispensable factors; and f, optional factors.

Bublitschenko recently made a constitutional study of a large number of eclamptic patients and found that they present certain constitutional characteristics, such as small stature and great body weight. Jsaaksohn, as well as Sserdjukoff and Melnikoff observed that eclampsia was particularly common in the so-called pyknic type (large head, chest and abdomen, with tendency to obesity, and relatively small extremities). Sserdjukoff and Melnikoff found that 3.5 per cent of pregnant women belonging to the pyknic group had eclampsia, and that the disease was also quite prevalent in the athletic type. According to these authors, a comprehensive study of the significance of constitutional factors in pregnancy, labor and the puerperium shows that eclampsia is many times more common in blondes than brunettes.

Aschner believes that the plethoric type is especially prone to eclampsia, and regards the diseases as resulting from a further development of the plethora and dyscrasia of normal pregnancy. He states that the three factors of first importance in the causation of eclampsia are: (1) extreme grade of plethora, (2) extreme degree of pregnancy dyscrasia (acidosis), and as a result (3) increased reflex irritability (pregnancy spasmophilia).

Mortality. Frankel in a paper entitled "The Present Status of Maternal and Infant Hygiene in the United States" giving the mortality figures for 17 states and the District of Columbia, or what is called the United States Birth Registration Area, states that the maternal mortality for 1917 was 663 deaths per 100,000 live births, and that for 1924, the figure was about the same. This means a total maternal

mortality of 1 in 150. Eclampsia and allied toxemias accounted for 165 deaths per 100,000 births, or approximately 1 in 600. Baker, in 1927, wrote that 27 per cent of maternal deaths in the United States are due to puerperal albuminuria and convulsions, while MacMurchy states that 22 per cent of the deaths in Canada are due to the toxemias of pregnancy. Frankel estimates that approximately 17,000 women die in the United States every year as the result of child birth, and as the toxemias account for about one-fourth of the total maternal mortality, we may conclude that between 4000 to 4500 women died each year from the toxemias of pregnancy.

This figure includes death from vomiting of pregnancy, chronic nephritis complicating pregnancy, acute yellow atrophy of the liver as well as eclampsia; and as eclampsia is responsible for about 60 per cent of the total, it is evident that it accounts for about 2500 maternal deaths a year in this country, a figure which is identical with that given by Burns in 1926. Provided the incidence and average mortality rate in eclampsia in all other countries is the same as in the United States, this would indicate that about 30,000 women die annually from eclampsia throughout the world. Should we take the incidence of eclampsia as given by Williams, namely 1 in 500, it would mean that in 56,000,000 births, the total number of eclamptic patients is 110,000 a year with a total maternal mortality of 30,000 or 27.3 per cent.

The maternal mortality in eclampsia varies in different clinics and in different countries and this will be taken up more specifically in discussing the treatment; but it seems to be a safe estimate that the maternal mortality rate approaches 25 per cent throughout the world.

Pathology. In 1843 Lever demonstrated that the urine of eclamptic patients contained albumin, and this led to the theory that kidney lesions were always associated with eclampsia. Traube and Rosenstein regarded the kidney changes as resulting from pressure of the pregnant uterus on the renal veins. Later Schröeder, Ingerslev, and others reported cases of eclampsia without albumin in the urine so that the uremic origin of the eclamptic convulsion had to be abandoned.

Autopsy will usually reveal the presence of renal changes, but the lesions are generally those of degeneration of the epithelium of the convoluted tubules, according to Williams. Prutz observed kidney changes in over 95 per cent in a series of eclamptic patients who came

to autopsy, but is of the opinion that the kidney lesions play a secondary part in the production of eclampsia, as they are for the most part too slight to be of great significance. Schmorl, Barr and others hold a similar view. Heynemann, on the other hand, is a strong advocate of the theory that kidney lesions are fundamental in the etiology of eclampsia. He believes that the condition in eclampsia is identical with the so-called kidney of pregnancy. Watson studied three cases of eclampsia and found profuse glomerulonephritis in all. Fahr has given an excellent résumé of the literature covering the kidney changes in eclampsia. In his own cases of eclampsia he observed renal findings suggesting a tubulo- and glomerulo-nephritis, in other words, primary degenerative changes in the tubular epithelium and glomeruli, as well as degenerative changes in the arterioles. He summarizes the pathology of the kidney in eclampsia as follows: (1) swelling of the glomerular loops, (2) albuminous degeneration of the epithelium, (3) degenerative (inflammatory) changes in the arterioles, (4) thrombotic processes in the vessels, especially the glomerular capillaries, (5) hemoglobin cylinders.

He further differentiates between the primary inflammatory processes, such as glomerulonephritis, in which there is a primary inflammation of the glomerular capillaries, and the kidney of eclampsia, as he does not regard the latter of an inflammatory nature.

Schwarz found similar changes in the kidney of eclampsia, swelling of the glomerular loops, albuminous degeneration of the convoluted tubules, hemoglobin cylinders, degenerative changes in the vessels and thrombi in the glomerular loops. He holds that the changes in the glomeruli are of chief interest, and seem to play the greatest part in the kidney lesions. The lumina of the glomeruli are narrowed as the result of the swelling and the vascular loops appear to be devoid of blood. Hyaline changes also occur, as well as fat depositions.

Although most cases of eclampsia present renal changes when studied in the autopsy room, it does not seem that the kidney lesions are characteristic of the disease, and are probably more the result than the cause of eclampsia. Furthermore, in patients who recover, the prompt return of the urine to normal inevitably indicates that the renal changes must be relatively trifling.

It is generally considered that peripheral necrosis of the liver

lobule is a characteristic lesion of eclampsia. Pilliet in 1888 described this hemorrhagic lesion in the liver of patients dying from eclampsia. His work was confirmed and elaborated in 1893 by Schmorl, who found typical lesions in the liver in every case of eclampsia studied. Williams, Opie and others regard areas of necrosis involving the periphery of the individual lobules and the portal spaces as characteristic of the disease, and do not hesitate to diagnosticate it merely from the presence of the lesion. At the same time they admit that the lesion is sometimes lacking in patients who have died from what was clinically eclampsia. For this reason they consider the lesions as a secondary manifestation, and not as the cause of the disease. In a recent article, Bell throws doubt on this concept and states that there is little agreement in the liver lesions in eclampsia. He observed passive congestion, localized infiltration, acute yellow atrophy, infarction, hemorrhagic necrosis, and cellular infiltration of the portal spaces in his cases, but found no typical lesion in all of them. He concludes that eclampsia is not dependent upon any one type of hepatic lesion. Levy-Solal and Tzanch are also of the opinion that the pathological findings in eclampsia are not characteristic and constant, and they consider that eclampsia is not caused by renal or hepatic disorders.

Fahr describes the liver of eclampsia as presenting typical changes localized in the periphery of the lobules, which are identical with those described by Schmorl, and which are characterized by the appearance of thrombofibrin in the portal capillaries, or capillary stasis, and the formation of blood spaces and hemorrhages, with cell destruction of the parts involved. Degenerative changes in the parenchyma, such as hyaline and fatty deposits, vacuolization, lymphocytic infiltration and more rarely bile stasis and small bile thrombi are also seen.

The brain has been carefully studied in many cases of eclampsia. Oedema, hyperemia, anemia, thrombosis, and softening are among the findings reported. Galy-Gasparrou and Labor report a case of eclampsia in which the brain was very carefully examined, and in which they found small hemorrhages under the pia-mater and large hemorrhages at the falx-cerebri, with small clots in the ventricle. Although it should be remembered that Volhard thirty-five years ago had directed attention to similar changes, Levant and Portes state that the pathology of the hemorrhages in the brain associated with

eclampsia is obscure, and that no distinct case of medullary hemorrhage associated with eclampsia has been described.

It has also been supposed that the ureters show pathological findings in eclampsia; Halbertsma first pointed out that the ureters are often enlarged and dilated in eclampsia and supposed that the condition played an etiological part. Prutz, however, noted that the ureters were abnormal in only 37 cases out of 500 autopsies, and as this incidence is not much greater than in normal pregnancy, we agree with him in holding that dilatation of the ureters plays no part in the production of eclampsia.

Polak in analyzing 102 autopsies on eclamptic patients, found that the heart was involved in 94. The change usually consisted in a degenerative process of the myocardium, as described by Schmorl; but these are the results of the disease and not characteristic or pathognomonic.

Giant cells have been demonstrated in the capillaries of the lungs, and have been identified as masses of syncytium. Schmorl supposed that giant cells were associated with the etiology of eclampsia, but as they can always be found in the lungs of pregnant women dead from any disease, this view is no longer tenable, and their presence is assumed to be a result of deportation, which is now regarded as a coincident of every pregnancy.

Williams states that the main lesions in eclampsia are found in the liver, kidneys, heart and brain, but that with the exception of the lesions in the liver, the anatomical changes are not constant and characteristic.

Etiology of eclampsia. Zweifel has called eclampsia the "Disease of the Theories" and today this is still true. The earlier theories regarding the etiology of eclampsia are fully discussed in the various text-books on obstetrics, and will be referred to only briefly in this paper. In the 17th and 18th centuries eclampsia was regarded as a disorder of the nervous system.

In 1820, Merriman, writing about its etiology, regarded an overloaded state as the cause of eclampsia. In 1833, Wilson suggested that there was an association between an increased content of urea in the blood stream and eclampsia.

In 1840, Rayer described albuminuria and when a few years later,

Lever and Simpson discovered albuminuria in eclampsia, there developed the uremia theory of eclampsia. Freirichs believed that the sudden destruction of the urea in the body was its cause.

The following are some of the theories advanced: 1, Auto-intoxication. 2, Foetal elements. 3, Foetal metabolic products. 4, Placental products. 5, Bacterial invasion. 6, Endocrine disturbances. 7, Biological reactions. 8, Alterations in maternal metabolism. 9, Mammary toxemias. 10, Diet. 11, Amniotic fluid. 12, Physical chemical changes.

a. Auto-intoxication. Bouchard (1887) was the first to speak of intoxication or auto-intoxication and believed the blood of eclamptic women to be more poisonous than that of normal persons, and their urine less toxic than normal.

It has often been stated that the eclamptic blood is more toxic than the blood in normal pregnancy. Lash and Welker tested the action of blood serum proteins in normal pregnancy and in eclampsia, by injecting large doses intraperitoneally into animals, but they could find no evidence of increased toxicity of the blood serum proteins in the latter.

In general, there are two types of toxins that may produce toxic symptoms; first, those substances which are usually present in the body in definite proportions and which in the disease appear in increased or decreased concentration. To this group belong such body constituents as sodium, calcium, potassium, magnesium, etc. (2) The poison concerned may be a substance foreign to the body, and to this group would belong such substances as the split products of the proteins, for example: tyramine, histamine and ergotamine.

b. Foetal elements. In 1902, Veit advanced the theory that fragments of chorionic villi and foetal ectoderm entered the maternal circulation and acted as a poison which he called syncytio-toxin. This he supposed is normally neutralized by an anti-body called syncytiolysin, but when the former is in excess of the latter, eclampsia develops. He based this hypothesis on the fact that foetal ectoderm and fragments of chorionic villi are constantly entering the maternal circulation, and believed that he had proved his theory when he found that an emulsion of human placenta injected into the peritoneal cavity of rabbits caused death of the animal, which showed albuminuria.

Hull and Rohdenberg in 1914 suggested that when an excess of

foetal elements is thrown into the maternal circulation, it is autolyzed with the formation of an excess of leucin, which in turn injures the hepatic vessels with resulting thrombosis, cloudy swelling, necrosis and even autolysis of the liver cells. They also considered that the renal changes in eclampsia were probably due in part to other products of autolysis.

c. Foetal metabolic products. Fehling and Dienst advanced the theory that products of foetal metabolism cause eclampsia. The well known fact that death of the foetus in utero, or delivery, often results in cure of the disease, made it quite natural to suppose that eclampsia may be foetal in origin. The occurrence of intercurrent eclampsia, in which complete cure occurs without delivery, speaks against this theory. It is generally believed that the death of the foetus in utero during eclampsia is followed by cure, but Maurice and Powilewicz in studying 94 cases found that in only 23 cases did the toxemia clear up after the death of the foetus. In contrast to this, they observed that in patients who gave birth to living children, the toxemic symptoms disappeared shortly after delivery. Seitz states the foetus causes the intoxication of eclampsia; while Hirst believes that the toxins of eclampsia originate mainly in the foetus and to a lesser extent in the placenta. Novak writes that the poison comes from incomplete and decomposed substances which are not completely excreted, in other words, a metabolic poison.

Certain investigators believe that because eclampsia can occur in cases of hydatidiform mole, the foetus can be ruled out as its cause. Frey described the case of a primipara, apparently six months pregnant, who from the fourth month onward had shown albumin in the urine. She had some bloody discharge and five convulsions before admission to the hospital. A cesarean section was performed, a hydatidiform mole removed, and the patient recovered. Similar cases have been reported by Folk, Olshausen, Hitschmann, Kroemer, Dienst and Sitzenfrey, and Gross. Frey suggests that the real cause of eclampsia is probably not the poison from the waste products of the foetus, but that the disease is due to a disturbed function and an internal secretion of the placenta itself. Wigger in 1928 reported the eighth case of eclampsia occurring in conjunction with hydatidiform mole, and holds that the foetus can be ruled out as the cause, but not the placenta,

as one still has chorionic epithelium in a mole. Consequently he does not agree with those who regard the occurrence of eclampsia in hydatidiform mole as an argument against its placental origin.

d. Placenta. Cheinisse states that the theory most generally accepted at the end of the nineteenth century, attributed eclampsia to the presence in the blood stream of a toxin coming from the placenta.

Since that time numerous experiments on the placenta and on placental extract have been conducted with the hope of finding the causal factor. Young has for many years claimed that the toxemias of pregnancy are especially associated with infarction of the placenta, and has developed his theory of placental autolysis to explain the etiology of eclampsia. Moreoever Young and Miller state that the placental degeneration is due to interference with its blood supply and that absorption of the placental poisons occurs through portions of the placenta attached to the uterine wall. They further reason that the toxemia may be associated with placenta praevia or premature separation of the placenta. Symptoms of eclampsia, they believe, are due to the absorption of broken down liver cells and possibly other cells, which are killed by the poison coming from the placenta. In cases of eclampsia where there is no placental infarction, they think the changes in the placenta are so minute that they cannot be detected by the microscope, but nevertheless give rise to sufficient toxin to cause the disease.

Several authors have studied the relationship of placental infarcts to eclampsia, but have failed to detect any definite connection. Williams believes that placental infarcts when present in cases of eclampsia should be regarded as accidental findings, or at least as secondary to the toxemic condition, and not as its cause as Young believes.

In 1901 Cocchi had produced lesions in the kidneys and liver, by injection of a placental substance. Since then placental hormones have been described, and the Abderhalden reaction has been developed. Bory, reviewing the work on placental toxins, concludes that physiologic syncytiolysis is the fundamental process in the causation of eclampsia. The presence in the blood stream of a substance which can activate the placental enzyme or toxin, and the absence of some inactivating substance, which normally protects the organism, he regards as secondary factors.

Gessner states that the occurrence of eclampsia associated with hydatidiform mole made it possible for Veit to develop his placental theory, but he argues that since the human race is the only one in which eclampsia occurs, although there are many other animals with a placental circulation similar to that of women, we are not justified in concluding that the disease is caused by a poison from the placenta. Moreover in certain conditions large quantities of placental ferment may be thrown into the blood stream without the development of eclampsia. In chronic nephritis, for example, there is usually abundant infarct formation in the placenta and yet eclampsia is a rare complication of that condition.

Selitzky considers that the toxemias are caused by unknown toxins coming from the endocrine glands and particularly from the internal secretion of the placenta, or from a functional modification of ovarian secretion.

Ishikawa made an alcoholic extract of the placenta of the rabbit and tested its toxicity. He came to the conclusion that an injection of such an extract, as well as of the foetus, produces anti-bodies in the rabbit and that proteins favor their formation. Oettingen and Schwoerer take issue with Obata, who holds that eclampsia is nothing but an intoxication from a placental poison. These authors do not believe in a specific placental toxin, but consider that eclampsia is due to the action of a by-product of metabolism.

In a series of experiments on artificial placental circulation, Dellepaine showed that the placental tissue possesses proteo-clastic properties which break down complex nitrogenous molecules into amino-acids, and that when large amounts of them are present the placenta causes their disappearance. He found no corresponding increase in ammonia and therefore reasoned that the amino-acids were elaborated synthetically. From his experiments he further concluded that the placenta manifests slight ammonio-genetic, as well as ureo-genetic activity. Zweifel found that the injection of foetal and placental albumin from one animal into another, of the same species, did not cause a hypersensitiveness as one would expect in the development of anaphylaxis, and consequently concludes that eclampsia is not due to such a reaction.

Stern, Lokchina and Falk tested the permeability of the placenta in

rabbits and rats and noted that colloids do not pass from the placenta to the foetuses. The crystalloids similarly do not pass through, except in very early pregnancy. They also noted that inhalation of carbon-monoxide so changed the permeability of the placenta that crystalloids would pass through it, while colloids were held back. Soli suggests that there is a possibility of the direct escape of foetal blood into the maternal circulation, because in eclampsia he noted an alteration in the villous capillaries, with diminished resistance of their walls. For this reason he holds that eclampsia is probably an anaphylactic reaction. Aranjo, on the other hand, regards the placenta as a protective mechanism both to the mother and to the foetus. It has a glycogenetic function, like a sort of uterine liver, which decreases during the later months of pregnancy when the foetus can take care of its own carbohydrate metabolism. The passage of undecomposed fat is impossible. He does not believe in a placental poison itself, but thinks that in certain cases the placenta may be insufficient and therefore fail to act as a protection to the mother, and that this insufficiency may be raised by the injection of placental extracts. Chappaz also regards the placenta as something more than a mere passive filter, and considers it as an actual regulating mechanism determining what substances shall pass between mother and child. Moreover, it seems well established from the work of Slemons and Stander, Tyler and Underhill, Mendel and Daniels, Wesson, and others that the placenta is impenetrable to fats and lipoids. Amino-acids and carbohydrates, on the other hand, pass from mother and child, and from this it would appear that the placenta acts simply as a semipermeable membrane.

e. Infectious theory. The bacterial origin of eclampsia was suggested in 1884 by Delore and Rodet, and since that time numerous writers have reported the finding of various bacteria in the urine and blood of women suffering from eclampsia. At present, however, no one seriously believes that there is any basis for regarding eclampsia as due to any specific bacterium.

Talbot believes that the toxemias of pregnancy are always associated with focal infection, and holds on the basis of clinicial observation that bacteremia, pyaemia and retro-placental abscess are frequently associated with the toxemias. Ivens is also a firm believer in the infectious origin, and recently Keller further expanded this theory and

gave the detailed account of eleven cases of eclampsia in which the urine showed bacterial growth. He states further that "with all the various theories of eclampsia and the site of its origin, the only organ which is constantly involved is the kidney. In 289 cases observed there were kidney symptoms in every one and pathological changes in all that went to autopsy. DeLee states the theory that eclampsia is due to an intoxication, is a toxemia, is most generally accepted, while it is admitted that the source and nature of the poisons are unknown. If we knew whether the toxemia came from the liver, the foetus, the placenta, the intestines, the general metabolism, disturbed glandular balance, from bacterial activity or from any other source, it would help our treatment immensely, but as yet we are groping blindly, empirically. However up to the present time no one has been able to isolate a germ that could be called causative."

Loomis writes that it is reasonable to assume that irritation from chronic sepsis may be a factor in lowering kidney and liver function and so play a rôle in the production of eclampsia. He lays special stress on dental abscess as a possible source of chronic sepsis, and although he does not believe that the dental abscess is the cause of toxemia, it may readily play a very important rôle.

f. Endocrines. During pregnancy the thyroid gland hypertrophies, and there is also evidence of anatomical changes in some of the other endocrine glands. Many attempts have been made to associate eclampsia with one or other endocrine disturbance. Lang, Ward and others suggested that failure to hypertrophy on the part of the thyroid gland may lead to toxemia of pregnancy. Today there is no convincing proof that the thyroid is of etiological significance in the production of eclampsia, and the same may be said regarding the parathyroid, as will be seen under the discussion on calcium metabolism.

Williams and Wallis hold that hyperactivity of the corpus luteum is the cause of eclampsia. In both menstruation and pregnancy this hyperactivity stimulates the thyroid gland to increased activity. Sometimes there is overproduction of this substance, when it escapes into the blood stream, and according to them causes vomiting of pregnancy or eclampsia. These authors state that the presence of an excess of cholesterol in the blood in pregnancy is very significant, as it occurs about the fourth month and at the time when the corpus

luteum is most active. In eclampsia the hypercholesterolemia is more marked than in normal pregnancy, and it has been shown that injections of corpus luteum extract increase the cholesterin content of the blood. They regard the increased cholesterol content of the blood as an attempt by the body to neutralize the toxic substance which comes from the corpus luteum. They experimented on rabbits with extracts from fresh corpora lutea of the pig and the human being, and were careful that the solution contained no cholesterol, cholin, histamine, tyramine, or protein. Such extracts injected into animals produced lesions similar to those found in the kidneys of women dying from eclampsia; but, in view of the fact that we have already stated that the renal lesions in eclampsia are very variable in extent and probably entirely secondary in character, their arguments do not appear very weighty. They conclude that the corpus luteum contains a chemical compound which can produce necrosis in animals as well as other changes similar to those encountered in eclampsia; and that an overproduction of this particular substance is the cause of eclampsia. They were not able to find such a substance in the placenta or in hydatidiform mole.

Hofbauer advocated the view that hyperfunction of the hypophysis and adrenals, resulting from insufficient secretion of the ovaries, caused eclampsia. Küstner in testing the various sera as to their action on pituitrin, comes to the conclusion that while normal non-pregnant serum has no effect on the action of pituitrin, pregnant and parturient serum has a supporting but not an inhibiting action, while the serum during the puerperium has no supporting action, and contains substances that soon produce disintegration of the pituitary principle. The serum from women with eclampsia has a supporting action and only a small inhibitory action. From these results, the author concludes that eclampsia is caused by a hypersecretion of the posterior-pituitary lobe hormone, or by a deficiency in the antibodies for this hormone and perhaps for the hormones of the other endocrines. In more recent work on this subject, this author found that there are three substances in the blood which effect the action of pituitary substance; these are: no. 1 which helps the action of pituitary, no. 2 which inhibits the action of pituitary, and no. 3 which completely neutralizes the action of pituitary principle. His conclusions are that while in normal

pregnant serum there is a considerable amount of no 1, none of no. 2, and a slight amount of no. 3, in eclampsia, on the contrary, there is a very great amount of no. 1, and a small amount of no. 3. He thinks that the toxin causing eclampsia acts on the vessel walls, since the most important finding of eclampsia is hypertension, and that the toxin probably comes from a dysfunction of the endocrine glands, and most probably from a hyperfunction of the hypophysis.

It may be interesting to learn in this connection that eclampsia has been reported following the use of pituitrin. Van Cauwenberghe observed an outbreak of eclampsia seventeen hours after delivery in a multipara who previously had no albumin in the urine, but who had received an injection of pituitary extract at the end of labor. Weymeersch has also reported the eclamptic attacks becoming more frequent and more violent after using pituitary extract. But, as pituitary extract is routinely used after the third stage of labor in many clinics, without any appreciable increase in the incidence of eclampsia, such observations must be regarded as purely coincidental.

Kark discusses a possible analogy between acromegaly and eclampsia, and regards the latter condition as essentially an overfunction of a physiological process.

g. Biological reactions. Schmorl, Veit, Lubarsch, Williams and others have drawn our attention to the fact that throughout the entire period of pregnancy, placental or foetal cells enter the circulation of the mother, a fact which has led to two further theories concerning the causation of eclampsia. The first depends upon agglutination and hemolysis, and the second upon an anaphylactic reaction.

Dienst in 1905, tried to show that foetal cells invaded the maternal organism, and produced changes in agglutination in the blood. McQuarrie studied the question of iso-agglutination and found that the toxemias of pregnancy occurred far more frequently when the maternal and foetal bloods were incompatible. Allen, in a much larger series of cases, could not corroborate the findings of McQuarrie, and holds that while interagglutination might possibly explain the occurrence of eclampsia in general, as well as its greater frequency in multiple pregnancy, it seems difficult to understand its relationship to the greatly increased incidence of the disease in primiparae. Moreover, the interagglutination theory cannot explain the occurrence of eclamp-

sia with hydatidiform mole, since in the majority of instances the degenerated villi contain no foetal blood. Allen studied the iso-agglutination characteristics of the blood of 375 normal and 104 toxemic women and their new born children. He found no evidence that incompatibility is more frequent in toxemic than in normal pregnancy, as is indicated by the fact that it was demonstrated in 20.8 per cent of the normal, and in 21.1 per cent of the toxemic pregnancies. Likewise he could find no evidence of specific immunization of the mother against foetal corpuscles.

Gruhzit, on the other hand, found that in the majority of cases of eclampsia, foetal and maternal bloods were incompatible, and he further observed that the blood of the eclamptic had a high viscosity, which he believes is due to the passage of incompatible blood elements from the foetus into the maternal blood stream. This author further reasons that the high viscosity of the blood in eclampsia brings about a colloidal condition which can produce congestion, stasis and oedema, and which in turn brings about lowered body function. As a result of this lowered metabolism, the hydrolysis of proteins and the oxidation of carbohydrates are slowed down, resulting in an acidosis. High blood pressure is also a result of this new colloidal condition of the blood. Jarzew has also claimed that the increased viscosity of the blood is an important factor in the production of eclampsia.

Louros believes that a primary dilatation of the uterine vessels may cause an increased blood pressure in the periphery. He, therefore, regards the constriction of peripheral blood vessels in pregnancy as secondary to dilatation of the abdominal vessels, caused by stimulation of the vagus. In other words, we have to deal with a vagotonia. Louros and Schmechel produced dilatation of the blood vessels in the region of the uterus in rabbits, and then ligated the hepatic vein, with the results that eclamptic-like changes developed in the liver. Louros thinks there are two types of eclampsia. In the first type there is vagal stimulation from an anaphylactic condition, which is gradually produced and compensated for; while in the second type the compensation does not take place, resulting in a falling blood pressure. He calls this second type the anaphylactic form. He holds that the vagal stimulation is caused by a disturbance in the general metabolism, which starts in the foetus, and that a vicious cycle exists between

metabolism and the vegetative nervous system. Moreover, he believes that constitutional factors are of importance, because women subject to vagal changes are prone to eclampsia.

The anaphylactic theory was proposed by Rosenau and Anderson. The principle of this hypothesis is that foetal protein enters the maternal circulation and under certain conditions may cause an anaphylactic reaction, very similar to that seen in other well-recognized forms of anaphylaxis.

Levy-Solal and Tzanck produced death in animals by the injection of sera of eclamptic women. From these sera they isolated two active principles, an anaphylactic principle causing convulsions, and a toxic one which was less severe in action, the anaphylactic principle, belonging to the class of antigens. Levy-Solal described three types of eclampsia, kidney eclampsia, liver eclampsia, and anaphylactic eclampsia. He believes that there are many cases in which neither the kidneys nor the liver are involved, and these he believes may possibly be associated with disturbances of the endocrine glands. Lawrence likewise states that eclampsia is an anaphylactic reaction, and that the convulsions follow failure of antibody production. In support of his contention, he mentions the favorable results following attempts to raise the antibody production and to decrease the amount of foreign protein in the system. According to him, colonic irrigation, gastric lavage and morphine increase antibody production, while foetal death, delivery or venesection may control the convulsions by checking the production of foetal toxins.

h. Mammary. Sellheim suggested that the toxic substance causing eclampsia is elaborated by the mammary gland and that the disease is analogous with parturient paresis in cows. Indeed, he carried his belief so far as to amputate the breasts from a patient suffering from severe eclampsia. Shortly thereafter, Healy and Kastle announced a similar belief and stated that they could produce eclampsia experimentally by injecting into guinea pigs small quantities of colostrum from cows suffering from parturient paresis, and they even found liver and kidney lesions in their animals suggesting eclampsia. Williams is skeptical about their results. Wilson stated that there are the following differences between the two diseases: (1) parturient paresis rarely attacks primiparous animals, while eclampsia is particularly

common in primiparae, (2) parturient paresis occurs almost entirely postpartum, while eclampsia occurs antepartum, intrapartum and postpartum, (3) parturient paresis increases in frequency in direct ratio with the rate of milk production, while this is not true in eclampsia, and (4) there is a glycosuria in parturient paresis but not in eclampsia. Harding, Murphy and Downs in a manuscript sent to the author, and which will be published shortly, give an excellent review of the subject, and state that since the work of Wilson the mammary theory has fallen into disfavor, although there are still some investigators who believe that it may prove of assistance. Schmidt in 1897, showed that by the injection of a small amount of potassium iodide into the udder the mortality in parturient paresis may be greatly reduced, and the present practice of inflating the udder with air has almost entirely done away with the mortality of the disease. Greig and Browne have recently been experimenting to find a simple means of inflating the human breast, although Harding and his co-workers conclude that it is unlikely that eclampsia in women is analogous to parturient paresis in cattle.

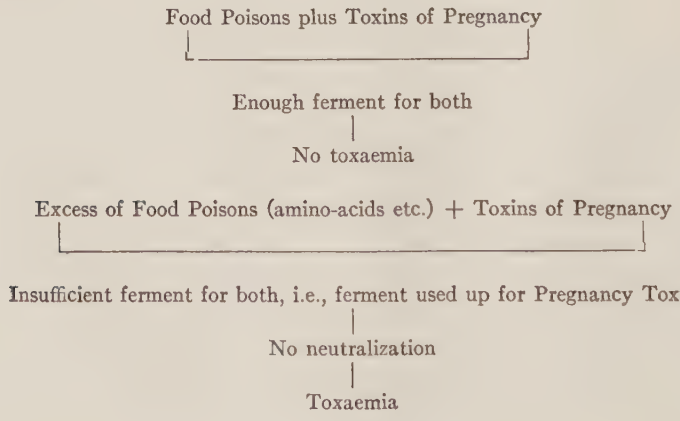
Pierrson on the other hand believes that the two diseases have so much in common, that it may be assumed that the same etiological factor underlies both. He believes that this consists in an over abundance of foetal nourishment in the maternal blood, and further suggests that repeated expression of the colostrum from the mammary glands might act as a prophylactic measure.

i. Diet. Diet has many times been under suspicion as the cause of eclampsia. Tweedy in 1913 suggested that ordinary food becomes poisonous during pregnancy and may give rise to eclampsia. He was led to this belief by the fact that women who partake of food, even in small quantities, often had a recurrence of the convulsions. Tweedy reasons that the antibodies in whole blood not only guard against bacteria, but also against products of digestion which may have entered the blood stream. He holds that the antibodies are stimulated by an antigen, which is present in colostrum, and that they have to hyperfunction, as it were, during pregnancy, as they are called upon to neutralize the foreign protein which gains access to the maternal blood stream from the ovum. Tweedy thinks that correctness of such a view is proven by the Abderhalden tests. Should the maternal

antibodies be unable to handle the food particles coming from the diet, as well as the protein coming from the foetus, the result may be serious and the patient develop eclampsia. He explains postpartum eclampsia on the theory that the mother's intestine contained food at the time when the convulsion developed.

Sellheim writes that eclampsia is more common in those who live on an animal diet, than in vegetarians. Reference has already been made to the fact that during the war the incidence of eclampsia fell, and this was attributed to the lack of protein and fat in the diet. Ruiz-Contreras argues that since eclampsia occurs less frequently among the poor than in well-to-do patients, and since the incidence was less during the war, when there was a shortage of food, particularly in meat and eggs, the cause of eclampsia must be sought in the diet.

In a personal communication Bethel-Solmons, regarding the etiology of eclampsia writes as follows: "We know that certain foodstuffs disagree with certain people, though they are perfectly harmless to others. Even the capacity of an individual to assimilate a certain food, changes, so that a food, which at one time may be taken with impunity, at another time acts as a virulent poison. Such changes are not uncommon in pregnant women. It is well known that all foreign proteins must be changed by the ferments of the body before they can be assimilated, and if they are absorbed without undergoing such change, they act instantly as most virulent poisons. Eclampsia may be explained in this way.


Food Poisons plus Toxins of Pregnancy
Enough ferment for both
No toxaemia
Excess of Food Poisons (amino-acids etc.) + Toxins of Pregnancy
Insufficient ferment for both, i.e., ferment used up for Pregnancy Toxins
No neutralization
Toxaemia

"On entering the body, this tox-albumin must be neutralized by the ferments (anti-bodies) already present, if its destructive effect is to be avoided.

"It is reasonable to conclude that the ferments which effect this neutralization are those which fix the amino-acids derived from food. These acids are not inexhaustible, as proved by the sickness and exhaustion which may follow the ingestion of certain food, such as eggs and lobsters. Similarly, we may suppose that the ferments are used up in the effort to counter the placental toxin; and the blood in this exhausted state can no longer deal effectively with additional food particles, the derivatives of which will now act as an irritant poison, destroying either directly or indirectly, the liver and kidney cells, and bringing on the well known symptoms of eclampsia. It must not be forgotten that the irritant poison present in the blood at this stage cannot be eliminated until its corpuscles get broken up into some less harmful product, such as urea. The absorption of these foreign proteins in this unprepared state, is the determining factor in eclampsia. This seems to us a complete explanation, which is controverted by no known clinical fact, and further, is certainly much more fruitful for purposes of treatment than any that has previously been put forward.

"Our views may be summed up by the following tables which show that if toxin enters the blood stream by chorionic villi in blood sinuses or from placental infarcts, and accompanied by excess of food, toxaemia results."

j. Renal origin. Volhard who has done a great deal of work on the various forms of nephritis, regards eclampsia as a form of acute uremia, and has proposed the term "eclamptic uremia." He believes that the convulsions may arise independently of the kidney function, and are due to general vaso-constriction, which is evidenced by the increase in blood pressure, which leads to ischaemia and oedema of the brain.

Paramore holds that the kidneys are always implicated in eclampsia, and that the convulsions are preceded by renal dysfunction. A diminished output of urine is a constant finding in the pre-eclamptic state, but he further reasons since women with chronic nephritis rarely develop eclampsia, that eclampsia must depend upon some other factor than inefficient kidneys, and that this may be found in an inefficient liver. Paramore believes that eclampsia is simply an uremia, in others words a pathological state characterized by a rise of nitrogenous waste or by-product in the blood, due to impairment of the liver or kidneys, or both. He is convinced that as the result of the rapid enlargement

of the uterus the intra-abdominal pressure is increased in pregnancy and more especially in primiparae, and he holds that the incidence of eclampsia is in relationship with this increased abdominal pressure.

Fitzgibbon believes that the pathological findings in eclampsia and other forms of toxemias of pregnancy are identical and that a subacute nephritis is present in all cases. The cause of the toxemia or eclampsia is an extra demand on the organs of elimination and the failure of these organs to keep pace with the excretory demand. Casamada, on the other hand, writes in 1928, that there is no association between eclampsia and kidney toxemias.

Poten in a recent article states that eclampsia is primarily due to renal insufficiency, and this is in turn due to dilatation of the ureters. He has devised a treatment which consists in performing a temporary ventral suspension of the uterus after delivery in order to avoid pressure on the ureters. He does not believe that eclampsia is caused by a placental poisoning, because of the fact that we very seldom, if ever, see eclampsia in the child, although the placenta is common to both circulations

k. Oedema theory. The hypothesis that oedema and actual anemia of the brain are the etiological factors in the production of ecalmpsia was first proposed by Traube and Rosenstein, in 1864. Straus and Widal think that salt retention causes oedema, and it is on this basis that Zangemeister has developed his theory that eclampsia is caused by oedema of the brain, and that in this disease the actual poison is water. He believes that the blood vessels become more permeable during pregnancy, so that water accumulates in the tissues with the result that the extra-vascular pressure increases, and that the intravascular pressure does not rise proportionately. With the increasing extra-vascular pressure there will be produced in the brain, decreased blood supply. This decreased blood supply means insufficient oxygen and imperfect nutrition of the brain cells, so that anaemic areas result. The process goes still further until areas of necrosis actually develop. Somewhere in the development of the latter, there will be an irritative stage in which the brain cells fail to receive the proper nutrition, and these "irritative" areas cause tonic and clonic muscular contractions.

Zangemeister thinks that at an early stage in this sequence of events water accumulates in the tissues, resulting in an abnormal increase in

the body weight. He consequently lays great stress on watching the increase of weight during gestation, and whenever it is much in excess of the normal limits, regards it as a danger signal. Damaged kidneys may play a part in the diminished output of urine and thus further accentuate the increase in body weight. It is interesting to note that all authors consider a certain degree of oedema as an almost universal accompaniment of pregnancy. Thus, Fink found it to some degree in 95 per cent of a series of 350 patients. He does not regard this as due so much to disturbed kidney function, as to an abnormal balance of the activity of the cells, as far as water metabolism is concerned. He thinks that this abnormal cell reaction to water may be associated with the action of various hormones and internal secretions which are presumably increased during pregnancy.

Wieloch made a study of 213 patients in order to determine the rôle of oedema in the causation of eclampsia. He believes that the primary cause of oedema is injury to the capillary endothelium. According to Zangemeister the increase in the blood pressure is of extra renal origin and is due to stimulation of the vasomotor centers through increased cerebral pressure, the latter in turn resulting from oedema of the brain. Wieloch concludes that the cerebral pressure theory explains the convulsons, as well as the headache, vomiting and fever.

l. Capillary spasm. Haselhorst examined the capillaries in normal non-pregnant, as well as in normal and abnormal pregnant women, and found that in eclampsia they are widened and lengthened, and that the blood corpuscles circulate through the capillaries in an irregular way with frequent periods of stasis. He has also demonstrated these changes by means of microphotographs taken three to ten weeks after delivery, and has also observed the occurrence of spasm in the capillaries of the eye during eclampsia.

Hinselmann, Nevermann, and Heynemann have made similar studies of the capillaries in eclampsia and have confirmed his results. Haselhorst believes that the spasm of the capillaries is the result of disturbance of the vascular nervous system, and is not due to an organic change in the vessel itself. Heynemann is also a firm believer in spasm of the vessels, but does not think that their cause has been definitely established.

Waschetko and Seletzky made studies on rabbits before and after

irritation of the cerebral cortex by means of an electric current. After the experiment had been repeated several times on the same animal at intervals of less than three days, they found that a small electric charge is required to cause convulsions; in other words, the cerebral cortex is labile to the electric stimulation. On the other hand, if the animal is allowed to rest for seven or more days after the experiment, as great a charge is required to bring about convulsions as at the first experiment.

m. Oxygen deficiency. Halbertsma believes that a deficiency of oxygen is the immediate cause of eclampsia; Rodenaker also regards a disturbance of oxidation as the exciting cause, and holds that the oxidizing power of tissues normally decreases towards the end of pregnancy and that in eclampsia it falls far below the normal level.

Hochenbichler regards eclampsia as an acidosis, due to lack of oxygen, and has demonstrated that a lowered bicarbonate reserve in the blood can be raised after exposure to ultra-violet light. He therefore recommends its use in treating eclampsia. Stander, in discussing the significance of the increased lactic acid of the blood in eclampsia, stated that whatever theory ultimately explains the etiology of eclampsia will have to take decreased or deficient oxidation into account. He considers this phenomenon as the most fundamental finding yet discovered in eclampsia.

n. Nervous origin. Elwyn has suggested a new explanation for the cause of eclampsia, which is based on his belief that there are two neuro-muscular mechanisms; one regulating vaso-constriction, and the other the contraction of the uterus. Both mechanisms are controlled from the midbrain and the impulses from these high centers travel by way of the thoracicolumbar outflow of the sympathetic nervous system. He believes that with the progress of pregnancy the irritability of the whole neuro-muscular mechanism for uterine contraction has become increased, and because of the proximity of the two centers, the increased irritability spreads to the center for vaso-constriction. This then leads to an increased irritability of the entire neuro-muscular mechanism of the arterial system, so that the arteries pass into a state of tonic contraction. As a result general arterial spasm develops and may lead to eclampsia. He regards this theory as particularly fitted to explain the mode of production of postpartum eclampsia.

Other theories, based on the effect the amniotic fluid may exert, on changes in the size of the protein particles, or on even more phenomenal changes, have been suggested, but unaccompanied by sufficient experimental or clinical data to warrant discussion in this paper.

o. Liver in eclampsia. At the end of the eighteenth century, Jurgens demonstrated that eclampsia was associated with liver changes, following which Pinard developed a theory that liver changes were associated with the etiology of the disease, "hepatotoxemie gravidique." The French authors of that time also spoke of "Insuffisance hepatique." Hofbauer in 1907 described what he thought was a typical liver of pregnancy, characterized by fat infiltration in the cells in the central part of the lobule, disappearance of glycogen, and dilatation of the bile channels, central vein and afferent capillaries, and consequently believed that it was normally in a state of diminished resistance. However, several later investigators failed to confirm Hofbauer's findings (Schickele and Heinreichsdorf). Opitz and Heinemann found that there is frequently an abnormal deposit of fat in the liver and on this basis it may be justifiable in speaking of a liver of pregnancy. Schickele has also shown fatty infiltration in the liver of pregnant animals. According to Basilevie and Jancenko, there is a disturbance of liver function in pregnancy, as shown by a decrease in the surface tension of the urine.

During the past ten years a great deal of work has been done on methods to determine hepatic function. Saitz studied the liver function in 25 normal pregnant women and observed that the excretion of uric acid is increased in 84 per cent, and ammonia and amino acids increased in 88 per cent. Bilirubin was increased in the blood in 8 per cent of the patients, while urobilin was increased in the urine in 64 per cent. He also noted an increase in cholesterol in the blood as well as a change in the carbohydrate metabolism as shown by the fact that a longer period is required for the assimilation of levulose, than in normal non-pregnant women. He does not know whether the changes are due to the liver, and concludes that one is not justified in definitely recognizing such an entity as the "liver of pregnancy." Kolmer, on the contrary, after examining a large series of livers microscopically, is convinced that there is such an entity. The phenoltetrachlorphthalein test developed by Rosenthal, has been used by many investi-

gators. In the toxemias of pregnancy, Smith found that retention of the dye occurs in eclampsia and pre-eclampsia, but that its degree does not appear to be an index of the amount of liver damage. Siegel substituted bromsulphthalein for the phenoltetrachlorphthalein test and believed that by its use he was able to differentiate between eclamptic and nephritic toxemias as he thinks that it gives valuable information regarding the amount of liver impairment. Schneiders and Rosenfield also feel that such liver function tests are of value in determining the amount of liver damage in the toxemias of pregnancy.

Piersol and Bockus found that the phenoltetrachlorphthalein liver function test gave fairly accurate information regarding liver damage, and whenever the excretion of the dye was delayed, they found urobilin in the urine. Naujaks also found that in the presence of liver injury there is always a delay in the excretion of the dye, but in the toxemias of pregnancy he was unable to find any parallelism between the severity of the disease and the result of the test. Krebs and Dieckmann also used the Rosenthal test but are not willing to draw any definite conclusions as to its prognostic value in toxemia, but are inclined to believe that it may afford an index as to the amount of liver damage in cases ot toxemia. King, reviewing the different liver function tests, states that the phenoltetrachlorphthalein, as well as its successor, the bromsulphthalein test, is of definite value, and that the degree of retention of dye seems to correspond with the severity of the toxemia. The van den Bergh test he found to be negative in pre-eclampsia and eclampsia, and he agrees with Piersol and Bockus that the Widal hemoclastic crisis test is of little value in toxemia of pregnancy. Eufinger and Bader disagree with King that the van den Bergh test is of little help in eclampsia. Their experiments showed that it reveals marked damage to the liver in the vomiting of pregnancy as well as in eclampsia. Steen also emphasizes its importance, as it makes possible the demonstration of hyperbilirubinemia at a time when it cannot be detected by any other means.

Herold used the method of Heilmeyer to test the pigment formation in the urine, in order to establish whether there is impaired liver function. In eclampsia he found a definite degree of liver damage, and is convinced that it is very slowly repaired as it is only late in the puerperium that the value of pigment substances is restored to normal.

Certain of the liver function tests have been tried in this clinic, and judging from the results obtained, as well as from the above account of the work of others, the author has come to the conclusion that very rarely do we gain information sufficiently important to warrant the institution of a routine liver test in patients suffering from toxemia of pregnancy. The chemical analysis of urine and blood, as we shall shortly see, invariably reveals the absence or presence of liver damage. Consequently, we have, perhaps somewhat prematurely, relegated liver function tests to the same class as the phenolsulphenophthalein test of kidney function in pregnancy toxemia.

Bile is composed of three main constituents: bile salts, cholesterol and bilirubin. According to Mann it seems that bile acids are made in the liver, though this has not been proven. We know very little about cholesterol metabolism. The other function of the liver is that of helping in protein metabolism and especially with reference to the purine bodies. Urea and uric acid are important nitrogenous by-products. Mann's experiments also prove that the liver is the main organ concerned in the destruction of uric acid. Among the unsolved problems, so far as the liver is concerned, is the part which it plays in fat metabolism. It is supposed to help in the transformation of fat into carbohydrate, although this has not been proven.

Mikeladse showed that in the toxemias of pregnancy there is an extreme degree of bilirubinemia. Saitz, Heynemann, Eufinger and Bader, Hermann and Kronfeld, Bakscht and Mikeladse, all regard the degree of bilirubinemia as of great diagnostic and prognostic value in toxemias of pregnancy. Mandelbaum, on the other hand, found that there is no relationship between the amount present in the serum and the degree of toxicity.

From the above it seems fairly well established that liver damage is one of the most constant findings in eclampsia. Whether this hepatic injury is "post hoc" or "propter hoc" is not yet known, although the author is inclined to believe that it appears very early in the development of the disease. Theories as to the agents responsible for such injury will be discussed under the following heading.

Chemical changes in eclampsia. From the account just given of the various theories concerning the etiology of eclampsia, it must be clear that no hypothesis, so far suggested, is accompanied by sufficient

evidence or experimental proof to be considered conclusive. We have seen in the earlier part of this review what marked maternal metabolic changes are always associated with normal pregnancy, and it is therefore natural to suppose that similar disturbances may play a rôle in the development of eclampsia. Consequently, in order to study this question, it becomes imperative to know how the mother's blood, urine and general metabolism are affected when she suffers from this disease.

A great deal of work has been done on the chemical findings in the urine and blood of eclamptic patients. Zweifel, in 1904, showed that in the urine the urea-nitrogen is lowered and the ammonia nitrogen raised. Stookey also found a low urea nitrogen (70 to 83 per cent of the total nitrogen) and a high ammonia nitrogen (5 to 10 per cent of the total nitrogen) in the urine as well as a high mono-amino-acid nitrogen and a positive para-dimethylaminobenzaldehyde reaction.

Hynd determined the optical activity of the urine in eclampsia and found it to be considerably less laevorotary than one would expect from the amount of protein shown. In 14 cases of eclampsia he noted that the protein in the urine was of two groups—one similar to serum albumin and the other approximately resembling cow's albumin, and concludes that in certain types of eclampsia it may be mainly lact-albumin, which affords a certain plausibility for assuming that eclampsia may be an anaphylactic reaction due to a foreign protein in the blood stream, or possibly, that the mammary glands may be an important factor in its causation.

Without reviewing in detail all the investigations on the composition of the urine, it may be stated that thus far no other marked disturbance has been noted in the eclamptic urine, with the exception of this shifting in the nitrogen partition, plus a decreased chloride excretion and an acetonuria. The pH of the urine has not been carefully studied in eclamptic patients. Zinsser made a biological study of the toxicity of the urine obtained from 9 cases of eclampsia. Upon injecting it into the peritoneal cavity or the circulation of guinea pigs, he found, contrary to the results of Pfeiffer, that death did not follow and so he concluded that there is nothing to warrant the assumption that a disintegration of albumin causes eclampsia, although Pfeiffer had stated that a discharge of albuminoids may produce an anaphylactic reaction.

p. Nitrogenous retention. More information, which may lead to an understanding of the etiology of the disease, has been accumulated on the chemical changes of the blood. It is generally agreed that the non-protein nitrogen of the blood is not increased in eclampsia. Where we do find a high non-protein nitrogen it is usually late in the disease and as a result of injury to the kidneys produced by the eclampsia, or of some factor dependent on the attack, as will be seen later. The same may be said with regard to the blood urea. J. T. Williams, in 1921, directed our attention to the fact that uric acid is definitely raised, and quite early in the course of the disease.

His findings have been abundantly confirmed by Caldwell and Lyle, Killian and Sherwin, King and Denis, and Stander. Hardy, Allin and Eagles showed that the blood uric acid was invariably raised when the patient was on a high fat diet and indicated that the change might be explained on the basis of decreased excretion. On the other hand, Cathcart, Graham and Poulton, and Umeda had all noticed a decreased excretion of uric acid in high fat diets.

Creatinine is the anhydride of creatine and a constituent of normal human urine. Very little is known regarding the excretion in eclampsia. The changes in the blood creatinine seem to depend entirely on the kidneys, and from the work of Mann and his associates it would appear that the liver does not play an important rôle in the creatin-creatinine metabolism. No outstanding disturbance in creatinine or creatine metabolism has been noted in eclampsia.

q. Inorganic constituents of the blood. Parathyroid tetany is always associated with a marked lowering of the blood calcium, and it is perhaps for this reason and because of the occurrence of convulsions in the two conditions, that so many attempts have been made to establish a connection between low blood calcium and eclampsia. Only the more recent contributions on this subject will be reviewed in this paper.

Calcium deprivation of the mother, resulting from the drain on her supply by the foetus, has furnished a wide field for speculation. As shown in the earlier part of this paper, the blood calcium is slightly lowered during the latter third of pregnancy, being at about the lower limit of normal.

Deschamps found the non-pregnant values to average 11.4 mgm.

per 100 cc. of blood, with limits of 10.4 and 11.5; in pregnancy from the second to the seventh month 10.6 to 11.97; at the eighth month 10.6 to 13.90; and during the ninth month 10.16 to 14 mgm. In eclampsia, the lowest figure recorded by this author was 9.4. Lemers likewise found a decrease in the blood calcium value in four cases of eclampsia. But on the other hand, Denis and King, as well as Stander, Duncan and Sisson, report no decrease, while Wodon, and Feinberg and Lash report normal values.

Hetenyi and Liebmann state that from 60 to 70 per cent of the calcium in the blood is in the form of ionized calcium; the rest is bound up with the albumin of the plasma or consists of non-ionized calcium salts. In 14 cases of pregnancy they found the calcium content to be between 9 and 12.6 whereas in the non-pregnant women it was between 10.5 and 12. During the last months of pregnancy there is a slight diminution in the blood calcium. All their findings demonstrate that in pregnancy there is an increased use of calcium, because of the requirements of the growing foetus and perhaps also because of a special property of the cells of the pregnant woman. Von Bodo and Liebmann examined the blood serum in eclampsia for ionized calcium, and concluded that while a decrease in free calcium ions of the blood might be responsible for the convulsions, such could not be demonstrated. They undertook this work because Lamers, Rissmann, and Kehrer had found a low blood calcium content in eclampsia and had explained the disease on the basis of a hypocalcemia. Bokelmann and Bock conclude that there is a slight decrease in calcium during pregnancy, and that during the puerperium it slowly comes back to a normal value; while the diffusible calcium in the serum is slightly increased at the end of pregnancy. Their figures are as follows: total calcium in normal non-pregnant, 9.62; first half of pregnancy, 9.75; second half of pregnancy 9.43 to 9.5 mgm. per 100 cc. of blood, while the dialysable calcium is 5.6 for the non-pregnant woman as contrasted with 5.53 to 5.54 mgm. for the pregnant. In three cases of eclampsia the total calcium was 8.08, 8.93 and 9.60 mgm. respectively, and the dialyzable calcium in the same patients was 5.45, 5.34 and 5.82 mgm. respectively. They conclude further that the total calcium, as well as the dialyzable calcium, is higher in the foetus than in the mother.

Odenthal thinks that the increased permeability in pregnancy may be associated with a disturbance between sodium and calcium ions. He found that the calcium coalescing effect during pregnancy is very slight, and held that it may be a factor in the production of capillary endothelium widening during pregnancy. Change in the pH and the relative shifting between K and Ca may be further factors in producing this change during pregnancy. From figures of all these observers one cannot conclude that a decrease in total blood calcium or in dialyzable calcium is associated with eclampsia.

Ivanyi, Rodecurt and Linzenmeier found that in eclampsia the Ca/P ratio is definitely decreased; Ca/P = 3.51 in non-pregnant; 3.46 in early pregnancy; and 2.53 in late pregnancy; while in eclampsia it was 1.87. This decrease of Ca/P in eclampsia according to their figures is due to an increase in phosphorus. Stander, Duncan and Sisson also noted a decrease in the ratio Ca/P or, as they expressed it, an increase in P/Ca, which is due to a high inorganic phosphorus value in eclamptic blood.

The other inorganic constituents of the blood, magnesium, sodium and potassium, are essentially within normal limits in eclampsia; while phosphorus is slightly elevated according to Rodecurt and Stander. The analyses of Denis and King also seem to indicate that there is no appreciable change in these elements, while the phosphorus and sulphur content of the blood are essentially identical in toxemic and normal pregnancies. One may, therefore, conclude that no marked disturbance in the inorganic elements of the blood takes place in eclampsia, except perhaps in so far as the ratio P/Ca is somewhat upset due to elevated phosphorus values.

r. Lipoids. Tyler and Underhill corroborated the work of Slemons and Stander, who showed that there is a definite increase in the total lipoids in the blood stream during normal pregnancy. Hellmuth also noted a hyperlipoidemia. Neither Hellmuth nor Slemons and Stander could find any difference in the lipoids in the toxemias of pregnancy or in eclampsia. They noted the same increase in total fats, in normal pregnant women as in those suffering from eclampsia. Ito and Kitamure found the cholesterol content of the blood to be decreased in diseases of the liver as well as in cases of nephritis. Adler and Lemmel also showed that the cholesterol content of the blood

changes in diseases of the liver, and regard the decrease of cholesterol and cholesterol-ester as indicating a disturbance of liver cells.

We may accordingly conclude that no characteristic change in the blood fats or blood lipoids is associated with the development of eclampsia. Whether the increase in fat, lecithin and cholesterol as the pregnant woman approaches term, may play a rôle in the production of ketosis will be discussed later. Up to date all attempts to connect the cause of eclampsia with a disturbance of blood lipoids have met with failure, unless the recent work on colloids should lead to more fruitful results.

s. Colloids. Colloidal chemistry has played a certain rôle in obstetrics during the past ten years. Since 1861, when Graham defined colloids as "substances which are not diffusible through animal membranes," there has been a steady development in the science of colloidal chemistry. Our old ideas of colloids have been completely changed by the work of Hardy, Jacques Loeb and others.

By the term hydrogel we denote such colloids as will solidify into a gelatinous mass with an abundance of water; and by hydrosol such colloids as are soluble in water. Colloids can usually be grouped into two classes (1) emulsion colloids, emulsoids or hydrophile colloids; and (2) suspension colloids. Proteins, starch and glycogen belong to the hydrophile class, whereas cholesterol is an excellent example of the suspension type of colloid. In an aqueous solution there is a relationship between the dissolved substance and the solvent in the hydrophile class, whereas in suspension colloids it is absent. The relationship in the hydrophile class is shown by measurement of the viscosity, which in the suspension colloids is not much altered. There is a further distinction between these two types of colloids—namely the rate of precipitation by electrolytes. Ready precipitation takes place by electrolytes in suspension colloids, whereas it is extremely difficult in hydrophile colloids. Colloids have also been classified according to their size; and particles of from 200 $\mu\mu$ (about the limit of microscopic vision) down to 1 $\mu\mu$, or 1 one thousandth μ, are said to be in colloidal state. This method of classifying colloids is, however, not very satisfactory.

The terms lyophile and lyophobe are also applied to colloids. A lyophile colloid has a tendency to unite with the dispersion medium, whereas a lyophobe has little or no tendency to become hydrated. By

the dispersion medium we mean the solution in which the colloids are present and by disperse phase we mean the particles of colloids in the solution.

Some colloids are called protective colloids and by this we mean that certain hydrophile colloids, which are precipitated with difficulty by electrolytes, have the power of protecting suspension colloids against the precipitating action of electrolytes.

A great deal of work has recently been done on the colloids of the blood during pregnancy and in the toxemias of pregnancy, and Eufinger particularly has shown that there is a definite alteration in the protein fractions of the serum during pregnancy. The ratio $\frac{\text{albumin}}{\text{globulin}}$ decreases from 2.6 in normal non-pregnant women to 0.81 in women at term; whereas the euglobulin and fibrinogen both increase as term is approached. He found by the Gerloczy reaction that there is a decrease in stability and an increase in lability of the plasma during pregnancy. Other colloids are precipitated by the very stable plasma of the newborn, whereas they are not precipitated by the plasma of the mother. Von Oettingen explains this on the basis that the very labile colloids of the mother act as protective colloids. Eufinger concludes from the work of Erich Meyer, Handovsky, Westphal and others, that the hydrophobe cholesterol fraction is of great importance as a tonic substance for the cell-membranes. We see an increase in the total cholesterol during pregnancy, but a percentage and progressive decrease of the important hydrophobe fraction up to the time of labor, a condition which, together with the protein phase-change towards the coarse dispersion side, is of great importance in the permeability and water metabolism of the cells. From the work of Overton we know that cholesterol, as a membrane-building substance, plays a part together with other lipoids on the cell-surface. There is an antagonism between lecithin and cholesterol, as the former loosens the cell-surfaces of the smooth muscle of the vessels, and the latter produces a thickening or hardening effect, which hinders the necessary lengthening of the muscle fiber after each contraction, with the result that the lowered permeability decreases the admission of water and of the swelling producing ions. When, in spite of the hypercholesterolemia in normal pregnancy, we do not have the

hypertonus, it is because of the firmer anchoring of the cholesterol in the plasma; in other words its quantitatively smaller availability furnishes an important regulatory mechanism in the pregnant organism for the maintenance of the normal tonus of the vessel. In Eufinger's opinion there results from these colloidal shiftings, which influence decisively the processes on the cell surface, the necessary lability and rapid adaptability of surface activity, which is required by the enormously varying demands of the pregnant organism. Clinically this lability in the behavior of the cell membrane is supposed to be shown in the form of the blood pressure curve in the altered response of the vessels to vasoconstrictor substances, such as adrenalin. Eufinger's work on the adrenalin blood pressure curve leads him to place in the foreground not only the state of the vegetative nervous system but also the local colloidal condition on the cell membrane as a significant influence on the form of the blood pressure.

Seitz also states that the plasma is more labile in pregnant than in non-pregnant women, although cholesterol is increased from 150 to 350 mgm. according to Chaffard, Neumann, Hermann and Hellmuth. Furthermore, there is a radical change in the composition of the cholesterol, since in non-pregnant women only 20 per cent of it is bound, while 80 per cent is readily shaken out, as compared with 40 per cent of bound cholesterol in the pregnant woman. The bound fraction is probably closely associated with euglobulin.

In eclampsia Eufinger found that $\frac{\text{albumin}}{\text{globulin}}$ ratio is still further decreased, the average value for normal pregnancy at term is 0.81, as compared with 0.21 for eclampsia. There is also a corresponding increase in fibrinogen in eclamptic patients. From these changes he assumes that there is a transfer of certain lipoids, which have been changed in their constitution, from the blood to the kidney epithelium, and that they are there eliminated. Seitz also believes that the change in the colloids of the blood is an etiological factor in the production of eclampsia.

In the toxemias there is, therefore, according to these authors, a greater disturbance in the distribution of protein fractions, the albumin being decreased and globulin and fibrinogen increased. Kaboh and Runge believe that the oedema depends on the lowering of the al-

bumin in the plasma. Seitz asserts that there are two types of eclampsia—one with very low albumin fraction in the serum (0.69 gram per cent) and the other type in which it is not so markedly reduced. In the first type the symptoms are severe and the mortality high, while the second type is mild, and is designated as "Labilitätseklampsie," by Seitz.

t. Carbohydrates. Without going into the chemical details of the methods of determining the blood sugar, it is essential, before discussing the sugar level in eclamptic blood, that it be pointed out that during the past ten years remarkable improvements in methods have been brought about by such chemists as Folin and Benedict. Stated briefly, the main desideratum in determining blood sugar is to employ a copper reagent which will not be affected by unknown non-glucose substances which have reducing powers. Formerly these bodies, as well as glucose, were included in the estimation, but gradually we have approached more closely to the true glucose value. This is rendered apparent by the fact that only a few years ago 100 mgm. of sugar per 100 cc. of blood was regarded as normal, whereas by the most recent method of Benedict this value has been reduced to about 60 mgm. It is, therefore, obvious that in comparing the results of different investigators one must know exactly what method of determination was employed before one can intelligently correlate findings.

Benthin, Walthard, Obata and Hayaski, Stander, Duncan and Sisson, Wieden, and others have reported hyperglycemia in eclampsia. Most of these authors explain the elevated blood sugar on the basis of the convulsions, since we know that muscular work raises the blood sugar. Stander and Radelet, however, found that the elevation often persists for an appreciable time after the cessation of the eclamptic convulsions, and Stander is inclined to think that added factors, such as changes in the hydrogen-ion concentration in the liver cells, may influence the production of a hyperglycemia. From figures submitted to him in personal communications from a number of clinics in this country, as well as from his own findings, which cover approximately 120 eclamptic patients, the author believes that the blood sugar values in eclampsia are sometimes within normal limits, often show a definite hyperglycemia, but never a hypoglycemia. He holds that in eclampsia there is a definite tendency towards hyperglycemia, in

contradistinction to Titus and his co-workers and Levy who report hypoglycemia. The following table shows the average, as well as the limits of, blood sugar level in eclampsia as observed in Baltimore, Pittsburgh and Los Angeles.

Blood sugar in eclampsia

AUTHOR	NUMBER OF CASES	AVERAGE	LIMITS
		mgm.	*mgm.*
Stander	94	102	44–190
Lazard	12	115	87–166
Miller and Martinez	19	105	75–181

Our findings in the above table were obtained by three different methods of determination, and where the latest Benedict method, which gives from 60 to 80 mgm. per 100 cc. blood for normal individuals, was not employed, the values were corrected to this standard. The findings from the other two clinics were submitted in personal communications, were not corrected and are based on 80 to 100 mgm. as the normal value.

Titus and his associates found that in serial blood sugar readings, during an attack of eclampsia, wide fluctuations occurred in the blood sugar within exceedingly short intervals of time. They found that the convulsive seizure occurred at levels which Titus calls relative hypoglycemia, and he holds that the fits are apparently the cause of the sudden drop in blood sugar; and that following them, there is usually a temporary rise in the blood sugar. Titus, Dodds and Willetts, in their recent contribution write:

"As a result of this and previous studies of toxemic disturbances of pregnancy, we are led to conclude that there is a relationship between all toxemias of pregnancy; that the difference between the hepatic lesions of the various clinical states is less distinctive than has generally been supposed; that there is no specific toxin; toxicoses of pregnancy, particularly eclampsia, are due to disturbances in maternal metabolism; and that the disturbance is one of carbohydrate metabolism, based primarily on a deficiency in carbohydrate intake plus increased consumption of carbohydrates which results in a depletion of the glycogen stores with consequential damage to the liver and its functions.

"This glycogen deficiency in the liver presently becomes equivalent to its partial 'extirpation;' the blood sugar values begin to seek hypoglycemic levels followed by frenzied efforts towards recovery, thus initiating the fluctuating waves noted in our charts; the convulsions which occur at certain low levels as the fluctuations become more and more violent are controllable, like the familiar hypoglycemic convulsions by glucose injections.

"The nephritis of preeclampsia and eclampsia, as well as grave hyperemesis, is not the forerunner but an incidental symptom and result of the intoxication.

"The insulin production of a nondiabetic pancreas may be temporarily in abeyance during a pregnancy intoxication as a physiologic responsibility to the lessened glycogen reserve in the body. Such a pancreas should respond to an injection of glucose as does any normal pancreas by an overproduction of endogenous insulin so that any additional insulin injected is an additional overdose."

The author has attempted to corroborate the findings of Titus, by studying the blood sugar at five minute intervals in eight eclamptic patients. The final results will be reported elsewhere, but it may be stated that he was unable to observe a relative hypoglycemia in any of them.

Scontrino determined the amount of free and combined blood sugar, and in normal pregnancy observed that there is an increase in the amount of free blood sugar during the first six months, a decrease during the last three months, and an increase during labor. In eclampsia there is an increase in the amount of free sugar, as well as of combined sugar during the attack. In this connection, it may be interesting to mention the work of John, who analyzed 22,808 blood sugar estimations in non-diabetic patients. He found 2452 that showed a blood sugar value below 80 mgm. per 100 cc., in 1791 it was 75 mgm. or below, while the lowest value was 30 mgm. per 100 cc. He holds that such a high percentage (11 per cent) of blood sugar below 80 mgm. per 100 cc. of blood, indicates that such low values are not so rare, and are apparently normal for the individuals concerned, as none of them presented any special complaint.

Bockelmann, Rother and others have assumed that it is possible for the human body to transform fat into carbohydrate, and furthermore

believe that this function takes place primarily in the liver. On the other hand, in a recent contribution Deuel and Milhorat state that there is no convincing proof that mammals are able to convert the fatty acid fraction of the fat molecule into carbohydrates. They were unable to demonstrate that acetic acid is a glucogenetic agent, nor was there any appreciable synthesis of glucose from sodium acetate when that substance was introduced subcutaneously or intraperitoneally into phlorhizinized dogs. In their control animals, the injected glucose was excreted almost quantitatively, and this would presumably indicate that, if glucose had been formed from the acetate, an extra amount of sugar would have been excreted in the urine.

Gottschalk and Nurnberger both believe that the glycosuria of pregnancy is due to a change in the permeability of the kidneys, and the former is convinced that the carbohydrate metabolism is decreased or slowed down during pregnancy. Lavake in 1916 suggested that a high carbohydrate diet might be of value in pre-eclamptic toxemia, as well as the administration of oxygen, as advocated by Stroganoff. Host writes that there is a curious and characteristic difference in the blood sugar during the first and second periods of pregnancy. Early in pregnancy, the kidney threshold for sugar is normal and the blood sugar is often remarkably high, so that when glycosuria occurs it is often associated with hyperglycemia and is not, as is generally believed, of renal origin. On the other hand, in the latter part of pregnancy, the blood sugar rise is usually very small, but the renal threshold is low so that glycosuria frequently occurs; and when it does it is probably renal in origin. This author suggests that the corpus luteum causes the sugar rise which is characteristic of early pregnancy, while the low renal threshold in the latter months appears to be dependent on the foetus or the placenta. Benthin, Walthard, Frey, Herold, Hellmuth and Guggisberg have all found low blood sugar values during the second half of pregnancy.

In labor there is usually an increase in blood sugar as was clearly demonstrated by Schmidt, Bickenbach and Jonen. These investigators studied the glycogen content of the liver and the muscles of dogs during pregnancy, and found in the normally fed animal a decrease in the relative weight of the liver at the end of pregnancy. The amount of glycogen in the liver of a normal well fed dog, getting

75 calories per kilogram of body weight, is approximately 6 per cent, whereas at the end of pregnancy it falls below 2.15 per cent. They also noticed that the fattest dog showed the greatest decrease in the glycogen content of the liver, which averaged 57 per cent of the normal value. They likewise found a similar decrease in the glycogen of the muscle throughout the body. They further analyzed for fat and observed that the fat content in the liver is sometimes but not always increased during pregnancy. They refer to the work of Delle Chiaie, who obtained similar results. In general, it may be said that when an increase of fat occurs during pregnancy it is not to be regarded as a degenerative process, but rather signifies a liberation of fat from the fat depots without injury to the cells. That there is a functional disturbance of the liver during pregnancy has not been definitely shown although these authorities believe that there is a change in the function of the "chemical organization" of the cells of the liver.

An increase in fat in the blood stream during pregnancy has been demonstrated by Capaldi, Herman and Neumann, Decio, and Slemons and Stander. Schmidt, Bickenback and Jonen regard this change as convincing proof that fat is liberated from the fat depots and is ready for utilization in the liver. Bockelmann and his co-workers have demonstrated that there is an increase in acetone bodies in the toxemias of pregnancy. Acetone bodies can be produced in only two ways, —either out of protein metabolism from amino acids, or from fat metabolism. The changes just mentioned, the glycogen decrease in the liver and muscles, the fat increase in the blood stream and liver, and the increase in acetone bodies—are regarded by Schmidt, Bickenback and Jonen as proof that carbohydrates are built in the liver from fat. As a sign of the liberation of fat for this purpose, we have the lipaemia, already referred to; and as a sign of the transfer of fat into carbohydrates, we have the acetone bodies. If the fat content of the liver becomes too great, which can be produced by a severe glycogen decrease and which is particularly common in very fat animals, then a disturbed liver function may develop.

The liberation of fat from the fat depots, as well as the splitting of fat, can go on undisturbed in the face of a severe glycogen shortage, but this is not true as far as the building up of new carbohydrates from fat is concerned, and when this occurs it is associated with the

production of acetone bodies. These authors state that the glycogen decrease must reach a certain degree before the process of manufacture of carbohydrates from fats is started.

To explain glycogen deficiency in both liver and muscle at the end of pregnancy, these authors invoke the influence of the vegetative nervous system. For example, Herold believes that vagotonia is responsible for the hypoglycemia at the end of pregnancy. Schmidt, Bickenback and Jonen, however, do not believe that it is responsible for the glycogen decrease noted in the liver and muscles, but hold that it can only be explained on the basis of an over-action of the sympathetic nervous system. Moreover, they believe that stimulation of the parasympathetics results in glycogen building in the liver, and as there already exists an increased stimulation of that system during pregnancy, it is impossible to explain the decreased glycogen in the liver at the end of pregnancy as the result of vegetative nervous disturbances. Consequently, we must seek another explanation, and these authorities hold that the decrease in glycogen can only be explained by a waste or burning up of the glycogen in the mother. The consumption of glycogen at the end of pregnancy must be more intense than in the non-pregnant woman. We do know that the respiratory quotient is increased (Magnus-Levy and Zuntz). Mahnert has shown that protein is spared during pregnancy and believes that with the burning of fat the carbohydrates are used in greater amounts. It is not so easy to prove that carbohydrates are wasted during pregnancy. The weight of the liver is of some importance, and that organ must do more work per unit of body weight than in the non-pregnant person. These authorities also examined the liver histologically and could find no changes at the end of pregnancy. There was undoubtedly fat infiltration in the liver cells, and particularly in their center, and such cells showed no glycogen. It would, therefore, appear from this work, that in normal pregnancy the liver shows signs of glycogen depletion, but that such a carbohydrate lack is the basis for the development of eclampsia has not been proven.

u. Acidosis. We know that in normal pregnancy there is a decrease in the CO_2 combining power, to approximately 44 volumes per cent, so that it is customary to speak of the "acidosis of pregnancy." Bock determined the hydrogen ion concentration for normal pregnancy and

found it to be 7.51 in the early months as compared to 7.52 for non-pregnant women. In the last months of pregnancy the pH of the blood dropped to 7.47, but during labor and the puerperium the average was 7.52. He concludes that during the last weeks of pregnancy there is an actual change in the reaction of the blood, and that this is brought about by the buffer capacity of the blood. He also believes that the amphoteric buffer substances, such as protein bodies, play an important part in this change. Schmidt and Wingen analyzed the gases of the blood and attempted to show that the large carbohydrate requirement during the latter part of pregnancy is partly met by the conversion of fat into glycogen, and that during this transformation acid by-products are liable to appear. These acid by-products require a certain amount of the alkali reserve of the blood for neutralization, and so lower the blood's capacity to bind CO_2 with a resulting lower alveolar CO_2 tension.

Gaebler and Rosen made a careful study of the acid base balance during pregnancy. They determined the alveolar CO_2 combining power, plasma bicarbonate, and the plasma pH, and found that during pregnancy the reaction of the plasma is slightly more alkaline than normal, though the plasma bicarbonate is lower than in the non-pregnant. Early in the puerperium the bicarbonate value increases, while the reaction of the plasma becomes more acid. The plasma pH values observed by them during pregnancy are not as alkaline as those found by Marrack and Boone, but the quantitative results are very similar. Vozza states that in the pregnancy toxemias, acidosis is the most conspicious finding, and that it is very pronounced in many eclamptic patients. He bases his conclusions on 200 determinations of the alkali reserve of the blood in various periods of normal and abnormal pregnancy.

MacNider found that in normal pregnant animals there is a definite tendency of the acid base equilibrium of the blood to become disturbed and that such a disturbance is more marked and more frequent in old than in young animals. He feels that this change is not dependent on renal injury and therefore is not a retention phenomenon. He concludes from a large series of experiments that, associated with gestation, there is a definite tendency towards failure to maintain a normal acid base equilibrium.

In eclampsia, the CO_2 combining power is still further decreased and it is not unusual to see values below 30 volumes per cent. The author believes that probably the lowest values for the CO_2 combining power ever observed sometimes occur in eclampsia, and he has noted it as low as 12 volumes per cent. Hasselbalch and Gammeltoft examined the blood of four eclamptic women and found in two cases that the fixed acidity of the blood was increased with an uncompensated acidosis, while in the other two cases the hydrogen ion concentration of the blood was normal. Bokelmann and Rother also found the CO_2 combining power in the blood lower in eclampsia than in normal pregnancy, and agree with Stander that the severity of the condition often seems to depend upon the degree of acidosis.

In eclampsia there is an increased production of acid bodies. Zweifel and Scheller found an increase in lactic acid in the blood and cerebrospinal fluid of three eclamptic women three to eight hours after a convulsion. These authorities are of the opinion that the increase in lactic acid in the spinal fluid may play a part in the production of the acidosis of pregnancy. Zweifel, Bockelmann, Kienlin, Loeser, Schultze, and Stander and Radelet have all reported increase in lactic acid in eclampsia. Some believe that this increase is associated with liver damage. In this connection it is interesting to note that Noah found that only in extensive destruction is the carbohydrate assimilating function of the liver disturbed to such an extent that there is an abnormal accumulation of lactic acid in the blood stream. Perger states that the increase in lactic acid is often due to a disturbance of the resynthesis of that acid by the muscles. The high lactic acid in eclampsia, may, therefore, be due to muscular work, damage to the liver cells, or to a disturbance in the resynthesis of glycogen from lactic acid following incomplete oxidative processes.

Amino acids have been proposed as a cause of eclampsia. Ewing and Wolf, because leucine and tyrosine had been found in the urine of eclamptic women, and because they themselves had found a decrease in urea and an increase in the undetermined nitrogen in the urine, suggested that amino acids were incompletely metabolized in the liver and were the cause of the toxemia. Murlin and Bailey found on the contrary, that not only the amino acid fractions but also the other

nitrogen fractions of the urine were usually within normal limits in eclampsia, and concluded that the nitrogen distribution in the urine was not of great help in the diagnosis of the disease. Furthermore, Losee and Van Slyke have analyzed the total amino acid nitrogen in eclampsia, and conclude that the toxemias of pregnancy can be attributed neither to failure in deaminization of the amino acids, nor to the moderate degree of acidosis observed in these cases.

In eclampsia, B-oxy-butyric acid may exert a toxic effect, not only because of its acid property, but also as a specific poison on the metabolism, as shown by the work of Harpuder and Erlsen.

In eclampsia, then, we have an acidosis, and usually a hyperglycemia. It is interesting to note that Bokelmann and Rother have shown that in two cases of eclampsia which came to autopsy, no glycogen could be demonstrated microscopically in the liver. Brinker has shown that it is possible to produce hyperglycemia in rabbits, by increasing the hydrogen-ions. He has also shown that the liver is not the only organ that plays a rôle in this mechanism; the liver, muscles, and also the kidneys will give up a great amount of sugar when placed in an acid medium, while an alkali medium will have the opposite effect.

Hamburger and Brinkmann demonstrated that the permeability of the kidneys depends upon the pH of the blood. From this consideration Bokelmann concludes that the hyperglycemia probably depends upon a disturbance in the acid base equilibrium. There are, of course, others who think that the changes in carbohydrate metabolism in pregnancy are due to the action of adrenalin; but from the work of Underhill, Cleissel and others, it seems that in human beings the adrenalin glycosuria depends upon the reaction of the blood, and that the glycogen mobilization action of adrenalin is weakened by alkalies and augmented by acids. Elias-Sammartino showed that by injecting adrenalin in rabbits, there developed a glycosuria as well as a decrease in the acid combining power of the blood; and that adrenalin will produce an increased amount of lactic acid in the liver. If, therefore, we accept the theory that there is a general hypertrophy of the endocrine glands, with a resulting increase in adrenalin secretion it becomes possible to explain the acidosis of pregnancy in an indirect way, namely

that the adrenalin causes an increased production of lactic acid with a subsequent increase in acidosis.

The acidosis undoubtedly has an effect on the blood vessels. Bokelmann states that when acid is introduced into the stomach of the rabbit, the alkali of the organism is decreased, and an increase in vaso-constrictor substances in the blood follows. Also, Kretschmer was able to increase the action of adrenalin by an intravenous injection of acid. Balin and Goldsmith have also shown that in acidosis the effect of adrenalin on vessels is increased, which is the reverse of what takes place in alkalosis, as shown by Druz and Fritz. But it is possible that the different acids may have a different effect. An increased CO_2 content of the blood never has a vaso-dilator action, while organic and inorganic acids have a vaso-constrictor action. On the other hand, we learn from the placenta perfusion experiments of Fleisch, Atzlar, Lehmann, and Schmidt, that the hydrogen-ion concentration has a vaso-dilator effect. As small a change in pH as 0.21 will alter the caliber of the vessel wall, according to these authors. The nervous system also reacts to a minimum change in pH, as shown by Bethe.

In eclampsia, if there is a great disturbance in the pH in the blood, as indicated by the work of Gammeltoft and Hasselbalch, the acidosis must act on the breathing center, as well as on other centers. The motor disturbances resulting in convulsions and coma, may be directly the result of this changed pH according to Kautsky. Bokelmann states that the changes in hydrogen ion concentration will produce hypertension, and if the peripheral vascular system is unable to take care of the blood flow, there will follow a decrease in the elimination of acid valencies; in such circumstances the amount of blood supplied to the brain increases and leads to congestion of the cerebral capillaries.

There is an antagonism between the various ions, but whether this plays a part in the acidosis of pregnancy or of eclampsia is not clear. We do know that an alkalosis leads to a decrease in calcium ionization, and it is possible that in the acidosis of pregnancy the ionized calcium increases at the cost of the bound calcium. In this connection the work of Rodecurt and Reginsburger is of interest. They found that the ultra-filtrable calcium and potassium decreased in eclampsia, while

there was an increase in sodium and in the $\frac{K}{Ca}$ ratio. The non-diffusible calcium is that type of calcium which is bound to protein, according to Rona. From the experiments of Kraus and others, it seems that the condition of the vegetative cells depends upon the equilibrium of anions and cations. Potassium has a para-sympathetic or vagal action, while calcium has a sympathetic action. Driesel states that the effect of acid bodies is to cause more calcium ions to be thrown out of the blood into the tissues. The decrease of the calcium in the blood, which is seen in sympatheticotonic conditions is explained on the basis that, as a result of the local acidosis, there is an increased amount of ions in the blood and this leaves the blood to go to the tissues. There further appears, according to Bokelmann, to be some connection or association between primary acidosis and decrease of blood calcium and the condition known as "sympatheticotonia." He states that there also appears to be a connection between the high blood pressure following increased adrenalin production and the tetanic contractions or convulsions; and it is even possible that there is a connection between the amount of hormone substances produced and the calcium, potassium and hydrogen-ions, as suggested by Zondek. There may also be a connection between carbohydrate metabolism and in particular lactacidogen, and the cations, as proposed by Emdem; calcium salts bringing about a synthesis and magnesium salts having an opposite effect.

Rossenbeck examined four cases of eclampsia for the chloride, sodium, calcium and potassium content of the blood and noted that the equilibrium between the sodium and chloride ions is definitely altered. He believes that the acidosis in eclampsia is caused not only by an over production of acid metabolites, but also by a definite decrease in alkali. This alkali deficit or alkalipenia further disturbs the processes of oxidation. The cause of this shifting in the ions is attributed by this author to a hyperfunction of the hypophysis, which causes sodium to leave the tissues. As a result of muscular contractions or convulsions, phosphoric and lactic acids are set free and these two acids could be drawn into the tissues in order to neutralize the accumulated sodium and so make it possible for the sodium to be

transformed back into the circulating blood stream. The acidosis of the blood stream could be combated by the increased washing out of the phosphoric acid in the form of secondary phosphates, according to Rossenbeck.

Beck states that in the pre-eclamptic state, the pH of the blood is the same as in normal pregnancy, while immediately before convulsions the pH is altered. During the attacks the pH may change as much as to 7.28 (pH normal blood 7.44), returning to normal during the puerperium. Beck believes that the change in pH is not associated with the cause of the convulsions, but is the result of muscular activity.

Although the complete acid-base equilibria formula has not been worked out for eclampsia, the data up to date seem to indicate that there is a marked disturbance in the oxidative processes, and that this is associated with an acidosis which may often become "uncompensated." We are as yet unable to state that this disturbance is the cause or the effect of the eclamptic outbreak, but it undoubtedly offers us one of the most promising fields for further work concerning the etiology of the disease.

v. Hypertension. As the increased blood pressure is one of the most outstanding characteristics in the majority of cases of eclampsia, many attempts have been made to explain its production on the basis of a toxin circulating in the blood stream. Volhard, Hülse, Becker, Hussey and others have worked on this theory. Volhard and Hülse have attempted to demonstrate that there are substances in the blood stream which make the vessel walls more sensitive to constrictor bodies in cases of hypertension. Hussey, on the other hand, believes that there are substances in the blood stream in hypertension and eclampsia which act directly as vaso-constrictor bodies on the vessel walls. These authors have speculated as to the nature of these different substances, and Volhard is of the opinion that they may be amines. In this connection it may be interesting to note that Hofbauer has suggested that histamine may play an etiological rôle in eclampsia. Tyramine has also been suggested by Johnston and Johnson as a causative factor in the toxemias of pregnancy. They base their contention on the fact that in a case of eclampsia, the vomitus, blood and placenta all showed the presence of tyramine. Stander, in attempting

to corroborate the findings of Hofbauer, was unable to produce the typical liver lesions of eclampsia in animals by the administration of histamine, and summed up his findings by saying "Peptone, albumose and histamine produce a blood picture suggesting anhydremia, and the evidence so far adduced both clinical and pathologically makes it improbable that any one of them is to be regarded as an etiological factor in the causation of eclampsia."

The search for, and isolation of, a toxin in the circulating blood, which will explain the etiology of eclampsia has so far been unsuccessful, and this field still remains an interesting and important one for further investigation.

Krogh in his studies on capillaries has found that colloids are not diffusible through the capillary endothelium, but that the capillaries may become permeable to them under certain conditions. Normally the capillary wall is impermeable to albumin and this is of great importance in the movement of fluid to and from the blood stream. Grzechowiak has measured the capillary pressure by means of the Kylin apparatus and found that while during normal pregnancy the capillary pressure is at first low and during the latter months approximately normal, it increases quite markedly in eclampsia.

It was formerly supposed that fluid passed from the blood vessels to the tissues by simple filtration. Recent work, however, indicated that factors other than simple filtration influence the passage of fluid. We now know that the rate of filtration through the capillary wall is directly proportional to the excess of capillary pressure over the osmotic pressure of the plasma proteins. These two forces—capillary pressure and osmotic pressure—work in opposite directions. Landis has stated that the increased permeability of the capillary wall may be accounted for by lowered oxygen tension, increased carbon dioxide tension or by local increase of permeability to the passage of protein through it. The lack of oxygen, in addition to indirectly affecting the tissue metabolites, also increases the permeability of the capillary wall and so permits the rapid filtration of fluid and the passage of plasma protein.

Yunoki and Uchino injected Congo red into gravid and non-gravid rabbits, as well as into pregnant and non-pregnant women and women

suffering from the late toxemias of pregnancy. In pregnancy they noted a delay in the speed with which the Congo red was absorbed from the serum both in rabbits and women, and the absorption was greatly retarded in women suffering from toxemia of pregnancy. Obata and Benda have recently advanced the theory that eclampsia is caused by a functional insufficiency of the reticulo-endothelial system. From the work of Ribbett and Goldmann we know that the reticulo-endothelial cells readily absorb colloidal acid-pigment granules. It would therefore seem that from the results of Yunoki and Uchino there is an insufficient function in eclampsia of the reticulo-endothelial system.

w. Summary. Eclampsia is very seldom associated with nitrogenous retention in the blood, and where the non-protein nitrogen is elevated it is probably the result of kidney injury caused by the eclamptic outbreak. The same holds true for the blood urea nitrogen. An increased uric acid and decreased CO_2 combining power are the outstanding findings in the blood chemistry in eclampsia. The blood sugar is sometimes normal, but is often elevated according to most authors; although some claim that hypoglycemia invariably accompanies the disease. The author believes that the weight of evidence is in favor of a normal or elevated blood sugar. Blood lactic acid is elevated in eclampsia. There is some controversy regarding amino-acids in the blood, but it appears that the disease is not associated with disturbed deaminization. The polypeptide nitrogen has not been satisfactorily worked out. Creatin and creatinine metabolism is not markedly upset. The blood chlorides show a disturbance where the disease is accompaneid by oedema. The only abnormal finding in the cations is a slight elevation in the $\frac{P}{Ca}$ ratio, due mainly to an increased phosphorus. The blood colloids reveal a disturbance consisting of a shifting in the protein fractions in favor of globulin, fibrinogen and euglobulin at the expense of albumin. Fats and lipoids show no greater disturbance than is noted in normal pregnancy. The very meager work on the hydrogen-ion concentration of the blood in eclampsia points to a true acidosis in some cases. No toxin in the blood or urine has been isolated. The only abnormal finding in the urine is a

slight upset in the nitrogen partition due to a decrease in the urea nitrogen. The various blood disturbances so far noted seem to be inter-related, and deficient oxidative processes probably play a major rôle.

Symptoms of eclampsia. The eclamptic entity is well known and a description of the symptoms, convulsions and semi-comatose or comatose condition seems unnecessary. It should be pointed out, however, that there are certain prodromal symptoms which serve as danger signals to those able to interpret their significance. Even in the absence of an increase in blood pressure or of albumin in the urine, the occurrence of very sharp epigastric pain, partial or complete amaurosis, or other visual disturbances, severe occipital headache and dizziness should make one suspicous of the pre-eclamptic condition; and all gravid women should be instructed to report immediately to their physician, should one or more of these symptoms make their appearance. It has been found that the diastolic blood pressure is often an earlier index of an impending eclampsia than is the systolic blood pressure. The earliest upset in the chemical constituents of the blood will usually be found in the uric acid and CO_2 combining power. The normal uric acid value ranges between 2 and 3.6 mgm. per 100 cc. of blood. Invariably one sees uric acid values of 5 to 8 or 9 mgm. in cases of eclampsia. Early in eclampsia or even in the pre-eclamptic state, uric acid may be as high as 5 or 6 mgm. per 100 cc. of blood. A patient presenting one or more of the above symptoms and showing an elevated uric acid content of the blood, with a CO_2 combining power below 35 volumes per cent, should be treated with caution and regarded as a potential eclamptic.

The eye findings in eclampsia present a very interesting field for speculation. It has been known for a long time that eclampsia is often associated with visual disturbances such as spots before the eyes, partial or even complete amaurosis. Santonsatso writes that in eclampsia the blindness may be associated with ophthalmological changes, as well as with a decrease in the intra-ocular pressure, but that in some cases no opthalmological changes can be noted. Cheney made fundus examinations in a large series of cases of toxemias at the Boston Lying-In Hospital, and feels that such routine examinations

are of distinct value. The most common eyeground findings are detachment or oedema of the retina, choked disc and inflammation of the choroid, acording to Hirsch. These conditions have a more favorable prognosis in the pregnant than in the non-pregnant woman. Hirsch also states that in eclampsia serious visual disturbances may develop, and yet the eye grounds may appear normal, and he thinks that the amaurosis in such cases is due to a disturbance in the visual centers of the brain. He found in 538 cases of eclampsia, 15 with total blindness and 13 with high grade amblyopia. Traymann reports a case of post-partum eclampsia with asymmetric hypertrophy of the hypophysis and thinks that the asymmetry of the sella turcica or perhaps hyperemia of one half of the hypophysis may be the cause of the hemianopsia observed. He advocates paying more attention to the eyes during pregnancy, as amaurosis may be the first sign of an impending toxemia.

It should be noted that eclampsia has also been described in cases of tubal pregnancy. Ebeler reported the case of a primipara 23 years old, from whom a right ruptured tubal pregnancy was removed. Within 10 hours after the operation she developed convulsions and the urine showed a large amount of albumin as well as casts. The patient died the next day with the diagnosis of eclampsia. He also refers to three other cases of extrauterine pregnancy associated with eclampsia.

Treatment of eclampsia. From about 1840 to 1870 the treatment of eclampsia consisted mainly in venesection, sedatives, cold packs or baths, but no obstetrical interference. Eden writes that from 1870 to 1890 the treatment was still expectant and that narcosis, diaphoresis and pilocarpin played a great part, but venesection was abandoned because Schroeder had pointed out that the blood pressure fell only temporarily after it. At about this time the current teaching was to the effect that the best results were obtained after the promptest possible delivery, which was effected by means of accouchment forcé and instrumental dilatation of the cervix. The maternal mortality for this period was over 30% where statistics were available. When the hepatic theory as to the causation of eclampsia came into vogue, Dührssen in 1890 advocated Caesarean section as the routine treatment for all cases of eclampsia, urging that the operation be performed as soon as possible

after the first convulsion. Shortly afterwards vaginal Caesarean section was introduced by him, and from that time on the radical treatment of eclampsia has been followed by many. At about the beginning of the present century a tendency developed toward the employment of more conservative methods of treating eclampsia because of the very high mortality following the use of vaginal and abdominal Caesarean section. These endeavors started in Europe and gradually came into use in England and the United States. Today there is still a great deal of controversy as to the relative merits of the two methods of treatment—the operative or radical and the medical, or conservative.

a. Pre-natal care. It has generally been recognized that pre-natal care is an important factor in preventing the occurrence of eclampsia, as well as in reducing the maternal mortality from it. In an excellent statistical study comprising over 42,000 deliveries, Rice showed that in patients who had received pre-natal care the incidence of eclampsia was only one in 1652 cases, as compared with a general incidence of about one in 200 deliveries in lying-in hospitals, as indicated above. The treatment of eclampsia may be divided into two types—the prophylactic and the curative. It is evident that a great deal can be done by careful pre-natal study of all pregnant women wherever this is possible. The frequent routine examination of the blood pressure, of the urine and of the patient's general condition, undoubtedly leads to the early recognition of a pre-eclamptic state or an eclampsia that may be pending. From our experience in this clinic we are convinced however, that prophylaxis alone cannot entirely prevent the outbreak of eclampsia, though it may be a great aid in reducing the incidence and the maternal mortality of the disease. Kaner, Williams and others are firm believers in the value of prophylaxis.

Nonaka, also an advocate of prophylaxis in eclampsia, suggests a diuretic-cardiotonic method of treatment in which he gives sodium theocine mixed with digalen and dissolved in a large amount of water; and his patients are made to drink this solution very slowly. He reports excellent maternal results.

b. Radical treatment. Until recently radical treatment was the general method of treatment and today there are three main schools,

each claiming that its method of treatment gives the best results. These are (1) Radical treatment; (2) Conservative treatment; and (3) A combination of radical and conservative. There are also various special treatments which will be taken up in detail.

Reuben Peterson is a very strong adherent of the radical treatment of eclampsia and recommends abdominal Caesarean section in treating ante-partum eclampsia. In 1914 he reported 530 cases of eclampsia treated by Caesarean section with a maternal mortality of 23.4 per cent. Waldstein reports 117 cases with a maternal mortality of 1.7 per cent. In 29 per cent of these cases he performed Caesarean section. Manna believes that in severe eclampsia, the best treatment is Caesarean section together with internal medication. Llames-Massini, who reports 92 cases of eclampsia, in 14 of which he performed Caesarean section with no maternal deaths, is a strong advocate of radical treatment.

Fuerst states that the best method of delivery in eclampsia is by transperitoneal cervical Caesarean section. In 238 cases he had only 9 maternal deaths, and as he believes that few of them could not be attributed to the method, he calculates his maternal mortality at 2.1 per cent. He does not place as much emphasis on the time consumed in performing the operation as does Wagner, who urges great speed in operating and states that no operation should take over twenty minutes. Stoeckel is a staunch believer in the Caesarean section treatment of eclampsia, and he reports a maternal mortality of 8.4 per cent in a series of 119 cases so treated.

Brodhead does not believe that abdominal section is always justifiable in the treatment of eclampsia. When one has to deal with a dead or non-viable child and the patient is in labor with a cervix partly dilated and is not in a hospital, Caesarean section is definitely contraindicated. He believes, however, that with more experience in a considerable number of cases Caesarean section may be the safest and most satisfactory way of treating eclampsia.

c. Conservative treatment. Plass in a very excellent review of the subject has compiled the following table to represent the results obtained in over 10,000 cases by these two methods, radical and conservative.

The Maternal Mortality of Eclampsia under the Active as Opposed to the Conservative Method of Treatment

AUTHOR	YEAR	NUMBER OF CASES	DEATHS	
			Number	Per cent
Active intervention				
Peterson	1911	530	124	23.4
Fruend	1912	551	95	17.2
Zweifel, P	1913	623	111	17.8
Peterson	1914	283	73	25.8
Brown	1916	6	1	16.7
Cragin	1917	251	71	28.3
Ruge II	1917	354	67	19.0
Brodhead	1918	302	53	17.5
Parke	1918	21	2	9.5
Poucher	1918	4	1	25.0
Brandt	1918	156	26	16.7
Kerr	1921	236	71	30.1
Stevens	1922	9	3	33.3
Eden	1922	93	25	26.9
Hirst	1922	17	3	17.6
Kellogg	1922	103	27	26.2
Zweifel, E	1923	204	38	18.6
Englemann	1923	59	18	30.3
Beck	1924	26	7	26.9
Langrock	1924	34	12	35.3
Lawrence	1925	5	3	60.0
King	1925	62	20	32.3
Wilson	1925	110	25	22.7
Davis and Harrar	1926	495	115	23.2
Greenhill	1926	78	6	7.7
		4,607	997	21.7
Conservative therapy				
Knipe and Donnelly	1916	59	10	17.0
Brown	1916	15	1	6.7
Cragin	1917	138	20	14.5
Ruge II	1917	213	31	14.5
Fruend	1917	168	24	14.3
Moran	1922	29	2	6.9
Stevens	1922	14	1	7.1
Solmons	1922	204	21	10.3
Hirst	1922	72	13	18.1
Zweifel, E	1923	107	8	7.5
Englemann	1923	244	27	11.1

AUTHOR	YEAR	NUMBER OF CASES	DEATHS	
			Number	Per cent
Conservative therapy—Continued				
Zweifel, P.	1923	317	27	8.5
Hingston and Mudaliar	1923	459	81	17.6
Beck	1924	38	7	18.4
Bunzel	1924	54	6	11.1
Langrock	1924	66	16	24.3
Hinselmann (Stroganoff)	1924	3,302	307	10.8
Lawrence	1925	28	7	25.0
King	1925	7	0	00.0
Wilson	1925	137	14	12.8
Alton and Lincoln	1925	4	1	25.0
Speidel	1925	11	2	18.2
Davis and Harrar	1926	149	23	15.4
Dorsett	1926	38	2	5.3
Lazard, Irwin and Vruwink	1926	103	14	13.6
		5,976	665	11.1

His tabulation shows that in the 4607 cases treated radically the mortality was 21.7 per cent, as contrasted with 11.1 per cent in 5976 cases treated conservatively. In other words, the mortality was reduced by nearly one half in the conservative series.

Plass writes

"At present there can be no question but that the regular treatment for eclampsia should be conservative, with radical surgical procedures reserved for the unusual cases with complications which themselves afford indications for operative delivery. One fact which should recommend this conclusion to you all is that conservative treatment may be carried out in the home with little added risk, whereas under such circumstances the danger from operative intervention is markedly increased. Ideally, all eclamptics should be treated in hospitals, but that is not yet possible, and it should be very consoling to the rural practitioner to know that he can, when necessary treat his eclamptic patient in the home by medical means and yet be following the best medical teaching.

There seems very little to choose between the various conservative treatments in vogue. They all give practically the same results in the hands of their exponents. Tweedy and the Dublin School have relied upon elimination and starvation. Stroganoff upon morphine and chloral, and Lichenstein upon copious venesection. The routines advocated by American

authors are mostly based around these three methods, but usually with rather essential modifications, dictated by some peculiar slant of the individual. The Stroganoff procedure is the simplest and therefore the most widely applicable, since it may be carried out away from a hospital and independent of any elaborate equipment."

It is impossible to review in detail the work of the various advocates of these two methods. In a discussion on the use of magnesium sulphate Stander compiled the following table indicating the end results obtained in 12 obstetrical clinics with radical and conservative treatment, respectively. From it one will see that although the conservative method of treatment usually gives better results as far as the maternal mortality is concerned, the fact cannot be ignored that certain clinics are obtaining excellent results with radical methods of treatment.

Gross maternal mortality in eclampsia

AUTHOR AND CLINIC	NUMBER OF CASES	TREATMENT	MORTALITY
Stoeckel—Leipsig	119	Radical	8.4
Leidenius—Helsingfors	250	Radical	14.2
Davis and Harrar—New York Lying-In	370	Radical	20.0
	149	Conservative (venesection)	15.0
Miller and King—New Orleans Charity Hospital	138	Radical	47.8
	38	Conservative (mod. Stroganoff)	15.8
Williams—Johns Hopkins Hospital	110	Radical	22.8
	198	Conservative (mod. Stroganoff)	13.6
Zweifel—Leipzig	394	Radical	18.5
	317	Conservative (venesection)	8.5
Powitzer—Berlin	245	Mixed	18.0
Engelmann—Dortmund	222	Mixed	10.4
Hochenbichler—Vienna	275	Mixed (quartz light)	18.1
Forssner—Stockholm	102	Conservative (Stroganoff)	10.8
Lazard, Irwin, Vruwink and McNeile—Los Angeles	138	Conservative ($MgSO_4$)	13.0
Dorsett and Dieckmann—St. Louis	94	Conservative ($MgSO_4$)	11.7

In this controversy as to the merits of the two methods some writers take very extreme views, for example Liepmann states that the only efficient treatment of eclampsia is by the method of rapid delivery and Stoeckel is similarly inclined. It should be pointed out that any statistics not covering a large series of cases, say at least 100, are of no great value, as in smaller series the numbers are too small to exclude accidental coincidences and consequently the conclusions drawn from them may be entirely misleading. Wilson in 1925 and Williams in 1927 analyzed the eclamptic statistics of this hospital. Williams inclines towards the conservative method of treatment as the result of the analysis of 275 cases treated by both methods. He reports a maternal mortality in the actively or radically treated cases of 22.8 per cent and in the conservatively treated cases of 13.3 per cent.

The Stroganoff treatment is perhaps the most widely used conservative method and the following is Stroganoff's own description of his method:

" 1. Upon admission: (a) Dark room with a minimum of noise. (b) Special nurse. (c) Examination or disturbance of patient only when absolutely necessary, and then usually under chloroform. (d) 0.015 (0.01–0.02) gram morphine hypodermically, while under chloroform narcosis;—usually about 10 to 15 grams of chloroform being employed.

2. One hour after admission: 2.0 (1.5–2.5) grams chloral hydrate per rectum with 100 cc. normal salt solution and 100 cc. milk. Should the patient be conscious the chloral hydrate can be administered without the use of chloroform, except where the patient has had one or more convulsions after admission; then about 10 grams of the anesthetic are used with each dose of chloral hydrate.

3. Three hours after admission: 0.015 (0.01–0.02) gram morphine hypodermically under 10 to 15 grams chloroform.

4. Seven hours after admission: 2.0 (1.5–2.5) grams chloral hydrate, as above.

5. Thirteen hours after admission: 1.5 (1.0–2.0) grams chloral hydrate, as above.

6. Twenty-one hours after admission: 1.5 (1.0–2.0) grams chloral hydrate, as above.

7. After each convulsion: Oxygen is administered as quickly as

possible. This is kept up until the breathing improves, usually about 5 minutes.

8. After three convulsions in the clinic: Venesection of not more than 400 cc. is resorted to.
9. In case of frequent convulsions: Chloroform and chloral hydrate to be used more energetically than outlined above.
10. No convulsions for thirty-four hours: If patient has been free from fits for twenty-four hours or longer after admission, and has not yet been delivered, she should be given about 0.5 grams chloral hydrate every eight hours for about three days.
11. Operative delivery is resorted to only when intervention becomes absolutely necessary for the sake of the child."

Since we know that chloroform produces central necrosis of the liver lobules and that in eclampsia we usually have to deal with a liver lesion, it does not seem logical to employ chloroform in its treatment. Furthermore from studies in this clinic it did not appear to us that venesection was of any great benefit since the fall in blood pressure following it was usually temporary, and in order to dilute the toxins effectively, if such were possible, one would have to withdraw 1500 cc. or more of blood. Consequently, the Stroganoff treatment was modified at the Johns Hopkins Hospital by omitting the venesection, and the following printed directions are at present routinely followed at that institution.

DISPENSARY

"1. Patients must be sent into the hospital whenever they show:
   (a) Systolic pressure of 150 or more and albumin.
   (b) Undue rise in diastolic pressure.
   (c) Any one of the above symptoms associated with severe headache, epigastric pain or pronounced edema.
   (d) Sudden amaurosis, even if none of the conditions mentioned above are present.
2. Patients with increasing blood pressure and definite trace of albumin must visit the dispensary twice a week. If they do not follow directions, Social Service must visit them *promptly*.

WARD SERVICE

Toxemias

1. In moderately sick patients when the albumin does not fall to below 1 gram per liter within a week, or when the general condition is not satisfactory, the induction of labor should be seriously considered.
2. Very ill patients will probably have induction of labor sooner, immediate induction when amaurosis develops suddenly, either with or without pain (epigastric). In primiparae with a rigid cervix, cesarean section may be considered.

Eclampsia

1. *Upon Admission.* Patients with frank eclampsia are:
   (a) To be placed in a quiet darkened room and to be disturbed as little as possible.
   (b) To have special nurse continuously until definitely out of coma.
   (c) To have $\frac{1}{4}$ grain morphia by hypodermic immediately.
   (d) To be catheterized, examined medically and obstetrically and bled for 200 cc. under nitrous oxide anesthesia if conscious. The venesection is done only when it is necessary to obtain a blood specimen for research work.
   (e) To be placed on one side, with foot of bed elevated so long as coma persists. Mucus to be swabbed from pharynx as it collects.
   (f) To have water freely when conscious. If patient cannot drink on account of coma or lack of desire, the intravenous administration of 500 cc. of 5 per cent glucose solution should be considered.
   (g) Not to be delivered until after cervix is fully dilated. Then by the simplest operative means, unless spontaneous delivery seems imminent.
   (h) No chloroform to be used.
   (i) Notify the chemical assistants as soon as patient is admitted, so that the necessary observations can be made.
2. *One hour after admission.* If comatose give 2 grams chloral hydrate in 100 cc. of normal salt solution, and the same quantity of milk per rectum. If conscious the chloral can be administered by mouth in 100 cc. of milk.

3. *Three hours after admission.*
   ¼ grain morphia hypodermically.
4. *Seven hours after admission.*
   2 grams chloral hydrate as above.
5. *Thirteen hours after admission.*
   1.5 grams chloral hydrate as above.
6. *Twenty-one hours after admission.*
   1.5 grams chloral hydrate as above.
   (a) While eclamptic patients are under treatment, the assistants and nurses must insist upon the greatest possible quiet on the fifth floor.
   (b) Catharsis, sweating or venesection in excess of 200 cc. must not be employed.
   (c) No change to be made in above schedule unless authorized by Drs. Williams or Stander."

McPherson, Zubrzycki, King, Speidel, Davidson, Davis, Beck, Bear and Bauch all advocate the conservative method of treatment. Clason in a recent article reports a mortality of 5.6 per cent in a series of 125 cases of eclampsia treated at the General Maternity Hospital in Stockholm by the complete or the modified Stroganoff-Zweifel method, except that pregnancy was interrupted in some of the cases where the symptoms in spite of treatment remained unchanged or became more severe.

Stroganoff himself has reported a large series of cases treated by his method. In his latest communication he states that 578 cases have been treated by his older method and 300 by his improved prophylactic method with a total maternal mortality of about 1 per cent.

From a study of Stroganoff's statistics, Stander found that about 70 per cent of his eclamptic patients had no convulsions before admission to the clinic and developed the condition only after admission; and of these 50 per cent had only one convulsion. He concludes that Stroganoff deals with mild and unneglected cases, while in most obstetrical clinics in this country the patient is usually admitted after having had several convulsions at home and is in a desperate condition. Katsuya, although a believer in the Stroganoff method, objects to the use of morphia, on the ground that it does not affect the cord reflexes, and in its place employs omnopon and scopolamine, which very quickly

inhibit the reflex centers in the cord and exert very litle harmful influence on the center of respiration. Instead of chloral he employs luminal, administered subcutaneously. His maternal mortality for the period of 1922–1925 in the Maternity Hospital at Tokyo was 5 per cent as compared with 20.8 per cent with the original Stroganoff method. Forssner likewise reports a maternal mortality of 8.4 per cent with the conservative treatment of Stroganoff and Zweifel, as against 19 per cent with active treatment.

A great advantage of the conservative over the radical treatment is that it affords us a means to treat intercurrent eclampsia, allow the pregnancy to proceed, and when intervention is necessary it may be done at an elective time. This does not mean that all cases of intercurrent eclampsia will respond favorably to conservative therapy, although it is advisable that this treatment be given a trial before operative procedures are resorted to.

d. Middle line treatment. There are some who believe that better results can be obtained by employing a treatment which is neither conservative nor radical. Zweifel changed from the active method of treatment to the so-called "Mittlere Linie" about 1911 and since that time this method of treatment has been extensively used. The treatment is expectant until it is evident that the conservative method is of no avail and active intervention is then resorted to. Should the patient be a primipara with an undilated cervix Caesarean section may be the procedure of choice, otherwise less radical methods for terminating pregnancy are employed.

From recent work in anesthesia it became apparent that chloroform, ether, nitrous oxide and even ethylene would produce lesions in the liver as well as changes in the concentration of the blood constituents, and furthermore that these changes in the blood constituents very closely simulated those observed in true eclampsia. It was for this reason that Stander suggested that possibly the poor results following active intervention in eclampsia may be explained not by the operative procedure itself but by the general anesthetic usually employed. He therefore recommended, when active intervention becomes necessary in eclampsia, that it be carried out under local or spinal anesthesia. This view is in agreement with the earlier work of Davis and DeLee. It is, furthermore, quite possible that a conservative method of

treatment, followed by operative intervention under spinal or local anesthesia whenever the patient does not improve, will give the best results.

e. Veratrum viride. In order to reduce the high blood pressure which is usually associated with eclampsia, some have used veratrum viride, which produces a rapid fall in blood pressure as well as in the pulse rate. About a half century ago Reamy of Cincinnati introduced the drug in the treatment of this disease. Stevens advocates the injection of 1 cc. as soon as the patient is seen, but considers it dangerous except in the presence of actual convulsions and high blood pressure. He reports a series of 25 personal cases with a maternal mortality of 16 per cent. Haultain and Bourne are both believers in the use of veratrum viride to control the blood pressure in eclampsia, and the latter advocates graduating the dose according to the height of the blood pressure, giving 1 cc. when the pressure is 190 mm. or above, and 0.25 cc. when it is between 140 and 155 mm. He states that after a large dose of veratrum viride the blood pressure may fall as much as 100 mm. Haultain also administers the drug repeatedly in doses ranging from 0.25 to 1 cc., and Smith and Rundlett likewise recommend it.

After the appearance of Cragin's enthusiastic report Williams for a time treated every other case of eclampsia with veratrum viride and the alternate case by the usual method, and found that the results in each series were practically identical. Consequently, the most he could say for it was that it did no great harm, and that it occasionally produced an alarming fall in pressure. It is doubtful whether such a fall in pressure is really beneficial and it should always be borne in mind that a high blood pressure may even be a protective mechanism. A generation ago veratrum was employed with a free hand in the treatment of eclampsia in this country, but at present its use has fallen into desuetude.

f. Venesection. Venesection has been one of the recognized methods of treatment for hundreds of years, and when the "toxic" origin of eclampsia was first advanced, blood letting was justified upon the supposition that it might serve to dilute or reduce the amount of "toxin" in the circulating blood stream. Some also advocate it as a means of reducing the blood pressure. Since phlebotomy was one of the earliest methods of treatment for many diseases, it was quite natural

that it should have been used to combat eclampsia. The amount of blood withdrawn varied from a few hundred cc. to 1000 cc. or 1500 cc., depending upon the severity of the attack and upon the boldness of the physician. Waldstein writes that if diet does not prevent oliguria, headache and ocular symptoms in a pre-eclamptic condition, venesection should be carried out, and in the definitely eclamptic patient he recommends the withdrawal of from 1000 to 1500 cc. of blood, following the venesection by the infusion of sodium chloride. He reports 117 cases of eclampsia so treated with a maternal mortality of 1.7. Eberhard recommends venesection of 500 cc., and Nevermann, Schlossmann, Zweifel, Lichenstein and Moran are among its advocates. Nevermann observed the blood stream and the capillary vessels during the bleeding and came to the conclusion that any improvement following it was due to a mechanical effect—namely the removal of venous blood containing toxins, which resulted in an increased blood flow throughout the circulatory system. Schlossmann also believes that the action of venesection in eclampsia is a detoxicating one, and that any reflex effect or lessening of the viscosity of the blood is secondary. He regards the fall in blood pressure following the bleeding as a measure of the effectiveness of venesection.

The use of venesection in eclampsia has been temporarily discarded in this clinic and Stander writes:

"I cannot help but think that the high blood pressure in eclampsia in many instances may represent a protective mechanism. Consequently, if a change in the semipermeability of the walls of the peripheral vessels plays a rôle in eclampsia, as I believe from experimental data which we are about to publish, it is safe to assume that the early and constant rise of the diastolic blood pressure is due to an increase in the peripheral resistance. If this state of affairs holds true, then a rise in blood pressure should facilitate osmosis and elimination. Additional evidence in support of such a view is afforded by the fact that there is such divergence of opinion as to the value of venesection in eclampsia, as well as by the fact that one often notices a remarkably sudden return of the blood pressure to its original high level after a venesection. Moreover, I cannot agree with Stroganoff in thinking that a venesection of 200 to 300 cc. can be of any material value in lowering the blood pressure or in the elimination of "toxins," and I hold that either it should not be employed at all, or if it is, that large quantities should be withdrawn (750–1000 cc.)."

g. Ammonium chloride. In order to treat the oedema which is often an accompaniment of eclampsia, Mussey suggested the use of ammonium chloride. He states that its use is generally followed by prompt diuresis, disappearance of oedema, marked loss of weight, lowered blood pressure and improvement of the patient, and that the improvement is usually greater and more lasting than that obtained by dietary methods. He also believes that the increased excretion of urine and the decrease in the oedema, with resulting loss of weight following its use, probably carries off from the tissues a sufficient amount of toxin to improve the condition. He warns that, although there is usually little or no increase in the blood urea in eclampsia, ammonium chloride should not be used without previous determinaton of the blood urea content and the alkali reserve, as these may become markedly increased following the use of the drug.

Iverson and Nakazawa believe that oedema is usually caused by a low colloid osmotic pressure. They found that in four cases with acute albuminuria there was a decrease in the colloid osmotic pressure sufficient to account for the oedema. They called attention to the fact, however, that increased hydrostatic pressure due to impaired circulation may also be an important factor.

h. Squatting posture. Lichenstein, believing that insufficiently oxidized protein substances may develop in a retro-placental hematoma and cause eclampsia by their absorption, claims that the best results in its treatment may be obtained by having the patient assume a squatting posture. He states that, as the intra-abdominal pressure is about three times as great in the squatting as in the recumbent posture, the former will tend to prevent the formation of a retro-placental hematoma, by making placental separation more difficult. This squatting posture is attained by having the patient's head and shoulders raised and the legs flexed by means of pillow supports. Hammerschlag in discussing the effects of this posture after delivery, states that it is of little value in the treatment of eclampsia.

i. Ultra violet rays treatment. Hochenbichler was the first to investigate the action of the quartz light in patients suffering from the late toxemias of pregnancy. He showed that the rays lower the blood pressure and also decrease any existing acidosis. Kermauner also recommends the use of ultra violet rays and believes that their good

effect may be due to their action on the vessel spasm in the kidneys, brain or skin. The number of cases thus far treated by this method is too small to justify any definite conclusions as to its efficiency; but as its application is simple and apparently harmless, further reports as to its clinical value will be awaited with interest.

j. Kidney decapsulation. The theory that eclampsia is due to failure of the excretory organs to eliminate any accumulating toxins of pregnancy, has led some investigators to remove the capsules of the kidneys in order to facilitate the function of those organs. Edebohls first performed renal decapsulation in a case of eclampsia in 1902, and since that time the subject has been reviewed by many writers, notably Pinard. Lübbert reported two cases where stripping off of the kidney capsule resulted in cessation of convulsions and complete recovery, and Cardwell and Brindeau both recommend it. Jullien reported a case successfully treated by decapsulation, but confesses that the indications for such intervention are very obscure, as some of the severest and most alarming cases often recover spontaneously and quite unexpectedly. He states that in 80 per cent of the cases decapsulation has given a good functional result, although the mortality ranges around 40 per cent. In general, it may be said that decapsulation is very rarely practised today in the treatment of eclampsia.

k. Lumbar puncture. According to the oedema theory of Zangemeister, intra-cranial pressure plays the most important rôle in eclampsia, and it may be relieved in either of two ways—by lumbar puncture or by trephining. Lumbar puncture was used in the treatment of eclampsia in 1904 by Krönig. Voron and Mantalin report three cases so treated after the usual treatment with sedatives and eliminants had failed. In each instance they obtained a clear fluid under normal pressure, and its removal was promptly followed by marked improvement, especially of the nervous symptoms, visual disturbances and headaches.

Wieloch recommends the use of sub-occipital trephining for both diagnostic and therapeutic reasons. He removes as much as 58 cc. of fluid and measures the tension according to the method of Kausch. He states that the pressure in the cisterna is normally about 150 mm. of water and approximately the same as in the lumbar canal. He found an increase in pressure in all his eclamptic cases except one,

which sometimes was as much as 100 mm. He states that in over 50 per cent of the cases the blood pressure falls after the puncture is made, and that diuresis was produced in 38 per cent. He goes so far as to recommend trephining not only in true eclampsia, but in pre-eclamptic patients as well. Years ago lumbar puncture was intermittently practised in this clinic, but the results following it were so little encouraging that its employment was abandoned.

l. Pulmonary oedema. As we all know, eclamptic patients sometimes succumb to pulmonary oedema, and Moore and Lawrence state that pulmonary oedema was the immediate cause of death in about one third of their fatal cases. Because of the high incidence of death due to this complication, these authors developed a method of providing continuous endo-bronchial aspiration, by means of an apparatus which is very simple and readily transportable, and whose employment they state presents no unusual difficulties to one trained in bronchoscopic technique. They advise that a bronchoscopist should be available in every obstetrical service.

Towards this same end Tweedy long ago directed attention to the necessity of preventing oedema of the lungs, by placing the patient in such a position that the nose and mouth are lower than the bottom of the chest, and turning her from side to side every half hour. To prevent aspiration of saliva into the bronchi and to retard the development of pulmonary oedema, it is customary in many clinics to have the foot of the bed elevated about 10 inches off the ground and to have the patient lie on her side with special instructions to the nurse to swab out the patient's throat whenever necessary.

m. Serum. Mayer in 1913 reported a case in which the serum of a normal pregnant woman was used to treat the eclamptic condition and was followed by recovery. A lumbar puncture was done and 5 cc. of fluid extracted, and this was replaced by the injection of 5 cc. of normal blood serum from a healthy pregnant woman. Recently McMahon recommended the use of blood serum obtained from eclamptic patients. This is given intravenously in doses ranging from 40 to 160 cc. He reports ten patients treated successfully by this method.

In the Boston Lying-In Hospital there has been developed a new serum method, which puts into practice the method of plasma-phaeresis which was developed experimentally by Abel some years ago.

Dr. Irving in a personal communication described this method as follows,

"To begin with it is not a serum treatment at all but a removal of a certain amount of the blood plasma; in other words a plasmaphaeresis done much as Abel, Rowntree and Turner did theirs on dogs. We proceed as follows. When an eclamptic is admitted she is at once started on the Stroganoff regime. She is then bled 1 liter into citrated solution under sterile precautions. The blood is then decanted into four sterile centrifuge flasks of 500 cc. each. Each flask contains about 250 cc. of citrated blood. The two flasks which are to be opposite each other in the centrifuge are balanced on the scales, using the necessary amount of salt solution for the purpose. The flasks are then covered with sterile paper caps and the whole number of them centrifuged for twenty minutes. They are then removed from the machine and the supernatant plasma pipetted off. We do this by using a sterile siphon tube which goes through one of the holes ina two hole stopper into a flask. Through the other hole goes a suction tube to start the siphon.

Enough normal saline to make the total amount in each flask up to about 250 cc. is now added. The corpuscles are now diffused in the salt solution by gently rotating the flasks. The flasks are balanced as before, centrifuged again for twenty minutes, and the supernatant salt solution siphoned off. In other words, we wash the corpuscles once. We then make the total quantity up to about 1 liter with normal saline and reinfuse it into the patient.

We do not feel that this is the only way to treat eclampsia. We do think, however, that it enables us to do venesections of large extent and leave our patients no worse for them. In most cases we find that the red count is no less after the plasmaphaeresis than it was before. If toxemia is caused by a toxin in the circulation it is probably in the plasma and not in the corpuscles. By removing a considerable portion of the plasma we feel that we are carrying out a rational procedure.

We have done this about fifteen times, and on two patients, twice. We have had only four eclamptics, all of whom recovered. We have also been able to reduce the blood pressure in preeclamptic toxemia, where, following delivery, there had been no reduction of the hypertension. It has done no good to the chronic nephritics. Our chief difficulty has been in getting enough eclamptics to use the method on."

n. Liver extract. Miller and Martinez have used liver extract or "heparmone" in the treatment of eclampsia. They write:

"If perchance the liver has a certain neutralizing function, which could be conserved by the addition of liver substance, however given, it would make little or no difference regarding the nature or source of the toxic agent of eclampsia provided the vital capacity of the liver could be increased at will to meet the emergencies of the situation. With this thought as a background we began (October 1926) the use of heparmone in the treatment of pre-eclamptic and eclamptic cases."

In their latest communication these authors report 43 consecutive eclamptic cases so treated, with a maternal mortality of 6.9 per cent. If they can continue to obtain such excellent results in a large series of cases the use of heparmone in the treatment of eclampsia will be certainly warranted. They report no untoward symptoms or results following the use of the extract, although in some women they gave as much as 275 cc. intravenously within a period of 12 hours. Their results are a stimulation to a further experimental and clinical test of the efficacy of this extract.

o. Magnesium sulphate. The intravenous administration of magnesium sulphate has been fairly extensively used in the treatment of eclampsia during the past ten years, and some authors, such as Lazard, Rucker, and Dieckmann, report excellent results.

Stander, in a recent review of the results obtained with this drug, concluded that the clinical experiences, as reported in the literature, are encouraging, but warned against the intravenous administration of too large a dose or too concentrated a solution of the salt. He advocated that when the drug be given intravenously, the strength of the solution should not exceed 10 per cent, and that at no time should the patient be given more than 20 cc. of such a solution, as in dogs he was able to produce liver lesions, and in some cases death, by the intravenous administration of too large an amount, or too concentrated a solution, of the sulphate. He considers that a total of 6 grams of $MgSO_4$, administered intravenously in 20 cc. doses of a 10 per cent solution over a period of about twenty-four hours, is within the limit of safety for an average-size woman, but that anything exceeding this may prove dangerous. The intramuscular administration of magnesium sulphate may be a safer procedure.

Lazard and his co-workers have treated a large series of eclamptics with this drug, with fairly good results, and are enthusiastic advocates

of its use. As further reports are published on the therapeutic value and toxicity of magnesium sulphate, we may be able to arrive at a truer evaluation of its worth in the treatment of eclampsia.

p. Diet. A great deal has been written about diet in eclampsia, and our attention was definitely focused on the amount and type of food the eclamptic patient received, when we learned that a marked reduction in the incidence of eclampsia had occurred during the war, at a time when the women were receiving less food than normally and when the diet consisted mainly of carbohydrates. Tweedy and his co-workers believe that the diet may even function as an etiological agent in the production of eclampsia, and consequently lay particular stress on the kind and amount of food patients should receive. Persson states that the treatment of eclampsia is one of diet and in the more severe cases venesection may be of help. Mastre recommends a diet low in protein and salt. Diet is undoubtedly of help in the prophylactic treatment or in the pre-eclamptic, but the average eclamptic patient that one sees in the hospital or at home, and who has had three or four or more convulsions, is usually semi-conscious and unable to take any food or fluids, even should it be desirable.

The Dublin School of obstetricians, under the leadership of Tweedy and others, have developed a particular method of treating eclampsia which has especially aroused our interest because Eden, in his careful report to the British Congress of Obstetricians and Gynecologists in 1922, showed that the maternal mortality following the use of the Dublin method was the lowest in the British Isles. According to Solomons, the method consists primarily in starvation, gastric lavage, bowel lavage, morphia, injection of sodium bicarbonate under the breast and close observation to prevent drowning or other accidents. In most cases the patient receives nothing but water for several days and should there be no improvement Caesarean section may be performed. The gastric lavage is continued until the water returns clear, when 2 oz. of magnesium sulphate solution are left in the stomach. The bowel lavage is given with the patient on her left side, with the tube inserted 18 inches into the bowel. Sodium bicarbonate, 1 gram to one pint, is used until the bowels are clear and then one pint of the solution is left in the bowel. Solomons writes that recently they have omitted the use of morphia and states that their average maternal mortality is about 10%.

q. Morphia. Morphia has been used for half a century in the treatment of eclampsia. Gustav Veit was the first to propose its routine use, and since his time this drug has been employed either alone or in conjunction with other methods of treatment. Stroganoff developed his method of treatment with morphia as its basis. Roe reported a series of thirty-two cases treated by morphia and colonic irrigation. This author uses 0.02 gram of the drug upon admission to the hospital, with half this dose again in another half hour, continuing with 0.001 gram at hourly intervals thereafter. Rouvier treats his cases in a similar way using small doses of morphia repeatedly at frequent intervals, and is enthusiastic as to its effect. Ferrere states that the maximum beneficial dose of morphia in the treatment of eclampsia is 0.12 gram but that larger doses may be given without danger to the patient. McPherson, at the New York Lying-In Hospital, has reported large series of cases treated with this drug. He gave morphia till the respirations fell to 8 per minute. In this clinic, some years ago, we did likewise, but at present never administer more than $\frac{1}{4}$ grain at one time nor more than $\frac{3}{4}$ grain in twenty-four hours.

It has recently been shown that morphia raises the CO_2 combining power of the blood, and this property, together with its sedative action, may explain the good results following its use in eclampsia.

r. Acidosis treatment. One of the most characteristic features in most cases of eclampsia is a marked acidosis, as has already been discussed above. The CO_2 combining power in the average case ranges around 30 volumes per cent, and in severely ill patients it is not unusual to see it drop as low as 15 volumes per cent. Following the work of Thalhimer on the use of insulin in post-operative acidosis, Stander and Duncan tried insulin to combat the acidosis of eclampsia. They followed the suggestion of Thalhimer and gave a protective dose of glucose, amounting to 2 grams of glucose per unit of insulin, in order to prevent the development of hypoglycemic symptoms. Insulin alone, as well as insulin together with glucose, has been quite extensively used during the past few years to overcome the acidosis in severe eclampsia. In general it may be said that when the CO_2 combining power drops below 30 volumes per cent, the patient is suffering from an acidosis which is probably the result of the eclampsia, and when it falls below 20 volumes per cent, the patient is usually desperately ill and is in urgent need of anti-acidosis treatment.

Collazo and Dobreff tested the action of insulin on the glands of external secretion and came to the conclusion that it definitely affects the basal metabolism, water distribution, colloidal condition of the cells, and such ferments as diastase.

Loeser reports 45 cases treated successfully with insulin and recommends that in eclampsia 20 to 40 units of insulin, together with 1 to 2 grams of glucose per unit of insulin be given. Vogt regards insulin and glucose as an excellent treatment for eclampsia. He administers from 5 to 50 units daily, combined with an enema of from one half to 1 liter of a 3 to a 5 per cent solution of dextrose. The acidosis of eclampsia may also be combated by drugs other than insulin. Wilson in a recent article recommends the use of sodium bicarbonate and places special emphasis on the CO_2 combining power as an index of the degree of acidosis. This author feels that while glucose will distinctly relieve an alkali deficit in either eclampsia or vomiting of pregnancy, it cannot be relied upon to raise the CO_2 combining power of the blood speedily enough in urgently sick patients. He regulates the dose of sodium bicarbonate to avoid producing an alkalosis, and combines the sodium salt with glucose injections wherever feasible.

Rodenacker believes that eclampsia is the result of a disturbance of oxidation and therefore recommends the use of insulin as a preventive in all cases where the oxidation is known to be disturbed. Schwab recommends the use of oxygen in severe cases of eclampsia because he believes that the intoxication from CO_2 is one of the principal dangers in eclampsia.

s. Summary. From this review of the various methods of treatment, it must be apparent that we have as yet no satisfactory way of combating this dreaded disease, whose average maternal mortality of 10 to 20 per cent is still far too high, while the foetal mortality, approximately 30 per cent, is much worse. We do not know the cause of the disease, and our treatment is consequently entirely empiric or symptomatic. At present the most logical and most promising treatment appears, to the author, to be one which is conservative, associated with radical interference under spinal or local anesthesia, should the conservative methods prove of no avail and the patient's condition become progressively worse.

Frequent blood analyses will reveal the presence or absence of a developing acidosis, and should the CO_2 combining power of the blood

fall to dangerously low levels (25 volumes per cent or lower) anti-acidosis treatment is urgently needed. For such a purpose, insulin with a protective dose of glucose, usually 30 units insulin and 60 grams of glucose in a 10 per cent solution, often acts efficiently.

In order to compare the different methods of treatment as practised in various lying-in hospitals, the author communicated with many of the leading obstetricians in this country and abroad. They were asked to state their views regarding the etiology, method of treatment and results obtained in eclampsia. The information gathered in this manner was most interesting and instructive. It was the general opinion that the cause of the disease is as yet unknown, and that it will probably be discovered in the course of metabolic investigations. The following table represents in brief the types of treatment employed.

CLINIC	TREATMENT
Bailey, New York	Conservative
Brindeau, Paris	Radical
Caldwell, New York	Conservative plus paraldehyde
Danforth, Evanston	Conservative plus venesection
Davis, Milwaukee	Conservative plus magnesium sulphate
DeLee, Chicago	Radical
Dieckmann, St. Louis	Conservative plus magnesium sulphate
Duncan, Montreal	Conservative
Ehrenfest, St. Louis	Conservative and occasional section
Foulkrod, Philadelphia	Conservative plus induction (rupture membrane)
Holmes, Chicago	Conservative
Johnstone, Edinburgh	Conservative plus colonic lavage
Keller, Philadelphia	Autogenous vaccines and middle line therapy
Lazard, Los Angeles	Conservative plus magnesium sulphate
Litzenberg, Minneapolis	Conservative plus venesection
Miller, New Orleans	Conservative
Miller, Pittsburgh	Conservative plus heparamone
Mussey, Rochester, Minn	Conservative
Newell, Boston	Conservative
Piper, Philadelphia	Middle line therapy
Plass, Iowa City	Conservative
Polak, Brooklyn	Conservative plus magnesium sulphate
Rucker, Richmond	Conservative plus magnesium sulphate
Schumann, Philadelphia	Conservative and occasional section
Solomons, Dublin	Conservative plus gastric and colonic lavage
Spalding, San Francisco	Conservative
Titus, Pittsburgh	Conservative plus glucose
Ward, New York	Conservative plus bag induction
Wilson, Rochester, N. Y.	Conservative

From this it will be seen that conservative treatment has in great part replaced operative interference in the treatment of the disease. It is also interesting to note that many authors are swinging toward a "middle line" therapy and are advocating Caesarean section under local or spinal anesthesia in certain selected cases.

Eclampsia in mother and child. Cases have been reported of eclamptic convulsions in both mother and child. Schwarzkoph in 1927 described 30 cases collected from the literature and Loebel, Kissinger and Laffont, and Gaujoux also report similar cases. It goes without saying that such cases are of great practical and scientific interest, as they indicate that the disease is due to the circulation of some "toxic" substance. At the same time great caution should be used in accepting them unless both mother and child have been subjected to autopsy and the existence of the characteristic liver lesions have been demonstrated in both by competent histological examination.

The mortality of children of eclamptic mothers is about 40%, according to Neugarten. He studied the fate of 81 living children of eclamptic mothers and found that after one year or more six of them had died, although the causes of death had no direct relationship to the maternal eclampsia. Of the 81 living children, 24 were re-examined in the hospital, one had suffered from convulsions, and all were entirely normal in physical and mental development.

In a recent contribution, Tunis analyzed the foetal mortality as recorded from different clinics in Germany, and prepared the following table.

Foetal mortality in eclampsia

	per cent
Zweifel	37
v. Franque	41
Lichtenstein	39
Zacheral	35
Weingarten	35
Bund	30
E. Martin	10
R. Freund	11.5
Heinlein	16
Stoeckel	8.6

He further compared the foetal mortality in Waldstein's Clinic with that of Esch, and found the former to be 10.8 per cent and the latter

40.2 per cent. He explains this marked difference by the fact that Waldstein employs active therapy while Esch adheres to the conservative treatment.

It will be seen that the foetal mortality is on the average about 30 per cent, and although our first consideration in the treatment of eclampsia is the welfare of the mother, it is hoped that the future may teach us to reduce further this appalling foetal mortality.

VI. Acute yellow atrophy of the liver

Acute yellow atrophy of the liver, also known as icterus gravis, is an acute necrosis of the liver cells accompanied by jaundice, disturbances of cerebration, and reduction in the size of the liver. According to Thierfelder and Quincke, about 60 per cent of all cases reported in the literature had occurred in pregnant women. The disease usually proves fatal, but, fortunately, is of very rare occurrence, as only a few hundred cases have been reported.

Etiology. The cause of the disease is unknown. Williams states that poisons, such as chloroform, arsenic, mercury and phosphorus, as well as certain diseases (syphilis, septicemia and congestion and cirrhosis of the liver) may be predisposing factors in some of the cases reported. Titus suggested that acute yellow atrophy of the liver may have the same etiology as eclampsia and vomiting of pregnancy. Certainly nothing definite is known regarding the etiology of the disease.

Pathology. The outstanding finding in acute yellow atrophy of the liver is the remarkable hepatic atrophy. The liver is often reduced to less than half its normal size, with a corresponding decrease in its weight, and a softening in its consistency. Central necrosis of the liver lobule is the characteristic histological picture, although the necrosis may extend throughout the lobule in the severe type of the disease. The interlobular spaces are not affected, the blood vessels and bile canals maintaining a normal appearance; associated with the hepatic lesions, one often finds acute changes in the epithelial lining of the convoluted tubules of the kidney, while the collecting tubules and glomeruli remain normal.

Symptoms. The disease may develop very suddenly, with sharp abdominal pain, headache and vomiting. Delirium, coma or con-

vulsions may follow quite promptly these prodromal symptoms. Jaundice develops rapidly and may become quite marked. The pulse and respiration are rapid; while, in contrast to the usual picture in eclampsia, the blood pressure is not elevated and the urine contains a slight amount of albumin. Instead of this rapidly developing course, the onset of the disease may be less acute and simulate pre-eclampsia. For a detailed description of the symptoms the reader is referred to the standard text-books on Obstetrics.

In the differential diagnosis between acute yellow atrophy of the liver and vomiting of pregnancy or eclampsia, the clinical course, and particularly the presence of icterus, the size of the liver, examination of the urine for leucine, tyrosine and the nitrogen partition, as well as analysis of the blood will be of definite assistance. We have already noted the changes in the urine and blood which usually accompany vomiting of pregnancy and eclampsia, respectively. It should also be noted that a general septicemia due to the gas bacillus may sometimes simulate acute yellow atrophy; and it is often very difficult to differentiate clinically between these two conditions. This was exemplified by a patient observed in this clinic last year, and Kohl in 1928 directed attention to the jaundice, cyanosis and the hematuria,which may occur in the former condition.

Stadie and van Slyke reported increased amino-acid nitrogen in the blood of a patient suffering from acute yellow atrophy of the liver. Wells studied the chemical composition of the liver in a case of acute yellow atrophy and found a considerable number of amino-acids, some of which had not previously been found free in human tissues. These amino-acids were leucin, tyrosin, glycocoll, alanin, pyrrolidin-carbonic acid, glutaminic acid, aspartic acid and lysin. Though histidin was also present, he was unable to isolate it. He obtained a total of 8 grams of amino-acids from approximately 700 grams of liver tissue, corresponding to about 12 grams of amino-acids in the entire liver. He agrees with Neuberg and Richter that all the amino-acids present could not have been derived from the autolyzed liver cells. There was also present a decrease in the diamino nitrogen. Sulphur was normal, while phosphorus was increased and the amount of fat, both free and combined, was below normal.

Oastler and Jacobi studied a case of acute yellow atrophy of the liver

and found that the blood had an increased urea content amounting to 50 mgm. The uric acid in the blood was 3.3 mgm. and the creatin about 2 mgm., while the CO_2 combining power of the blood was 40 volumes per cent. The patient's urine revealed the presence of leusin and tyrosin.

Treatment. Liver injury appears to be the outstanding characteristic of this disease, and from the experimental work of Whipple, Mann and others on hepatic damage, it would seem that the best therapy would be the administration of glucose. The glucose may be given intravenously in 10 per cent solution. The disease usually ends fatally, although Wilson and Goodpasture are more optimistic and state that recovery from acute yellow atrophy of the liver is probably more frequent than is generally believed.

The author wishes to express his sincere thanks to the many obstetricians, whose names unfortunately cannot be mentioned here, who were kind enough to furnish him with information regarding their views, laboratory findings and clinical results. He feels especially indebted to Dr. J. Whitridge Williams for many valuable suggestions.

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PAROXYSMAL HEMOGLOBINURIA

A Review

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HISTORICAL

Prior to the last half of the nineteenth century the disease entity now recognized as paroxysmal hemoglobinuria was not differentiated from conditions of quite different character. Owing to the absence of the necessary data in most of the early case reports and the probability that many of them dealt with intermittent hematurias or quite different types of hemoglobinurias, it is hardly possible to give to any one contributor the credit of discovery. Dressler (1854) described a case of what he called intermittent albuminuria and hematuria. He noted the fact that the color of the urine was due to hemoglobin and not to blood, but failed to recognize the rôle of chilling. His patient was a 10-year-old congenital syphilitic but the etiological importance of syphilis escaped him. The fact that the child had daily attacks which promptly ceased when quinine was given, even though it was in the month of January, raises the suspicion that this, like many of the other early case reports, dealt with malarial hemoglobinuria rather than true paroxysmal hemoglobinuria. Elliotson's (1831) patient, sometimes included as an early case of paroxysmal hemoglobinuria, was a man who had had ague and was quickly cured by quinine. The same is true of the patient recorded by Charles Stewart in 1794 under the title "Account of a singular periodical discharge of blood from the urethra terminating successfully." Success followed the administration of Peruvian bark. One of Harley's (1865) two cases which had "intermittent hematuria" made a quick recovery on mercury and quinine; the other seems unquestionably to have been a case of paroxysmal hemoglobinuria, but Harley was unaware of the

rôle of syphilis and the nature of the coloring matter in the urine. Pavy (1866) differentiated the disease from the hemoglobinuria of malaria, and Secchi (1872) confirmed Dressler's observation that it was hemoglobin and not blood which caused the dark color in the urine. Gull (1866) recognized the rôle of chilling but considered ague as one of the causes of the disease, but not the only cause. He thought that trauma might also be etiologically related to the occurrence of attacks. Rosenbach (1880) showed that an attack could be artificially produced by immersion of the patient's feet in ice water for 10 minutes. This has been called the Rosenbach test and is still of use both in the differential diagnosis from other forms of hemoglobinuria and for the purpose of studying the phenomena of a typical paroxysm. Lichtheim (1876) wrote an excellent report on three cases, in one of which striking vasomotor disturbances in the form of large wheals and prickling sensations were present during the attacks. Popper, S. Mackenzie and Murri also called attention to the vasomotor phenomena. Lichtheim recognized the fact that the urine was colored with hemoglobin and not with blood, that the paroxysms were brought on by chilling and, on the basis of Ponfick's pioneer transfusion experiments, he assumed that hemoglobinaemia occurred. He was led to this assumption also by the knowledge that water, arsenuretted hydrogen, and other substances causing hemolysis in vitro also cause hemoglobinuria. It had been thought previously that the hemolysis occurred in the kidneys. An English physician signing himself merely as "D" had suffered from the disease for 11 years and in 1879 published an account of his observations on himself. He emphasized the absence of parallelism between the rise of temperature and the other phenomena of the attack. He considered the "essence of the disease as a hurried and imperfect formation of blood corpuscles, which easily stagnate in the capillaries under cold, and quickly perish, and so are eliminated by the kidneys as a broken-down mass of blood-stuff." He was apparently unfamiliar, therefore, with some of the previous observations. Küssner (1879), by observing the color of the serum obtained with a cupping glass and comparing it with serum obtained during intervals between attacks, demonstrated that Lichtheim's assumption of intravascular hemolysis and hemoglobinaemia was correct. Ehrlich (1881), too, was interested in the mechanism of this disease. He

showed that by tying a ligature around the finger of one of these patients and immersing it in ice water hemoglobinaemia occurs locally in the ligated and chilled finger. This is known as the Ehrlich test. His first assumption was that the red blood cells were abnormally susceptible to low temperatures; further studies, however, with red cells alone exposed to cold compelled him to discard this view. He then concluded that in specifically disposed individuals under the influence of cold the vessel wall produces a ferment causing hemolysis. Clearly, therefore, he came close to discovering the Donath and Landsteiner reaction. In several of the cases recorded before 1880 a history or clinical manifestations of syphilis had been noted, but the etiological relationship between syphilis and paroxysmal hemoglobinuria appears to have been unsuspected until Murri emphasized the fact that of the 36 cases which he found in the literature 15 were unquestionably syphilitic. Götze (1884), from observation of a child with congenital syphilis and paroxysmal hemoglobinuria and from a review of the literature, also calls attention to the etiological relationship between the two diseases and this he seems to have done independently of Murri. Thus, before the end of the nineteenth century, despite the rarity of the condition, most of the clinical features were recognized. Many observers had contributed, each adding something but each one overlooking other aspects of the disease. It had been separated from the hematurias and from malarial hemoglobinuria, the etiological relation of syphilis was known; the rôle of chilling, the vasomotor phenomena, the occurrence of hemoglobinaemia, and the artificial production of attacks by chilling were well established. In 1894 Chvostek reviewed the literature very thoroughly and his monograph summarizes the existing knowledge and prevailing theories of the disease. He divided the disease into two groups of cases—(*A*) those in which the resistance of the erythrocytes is quite normal; (*B*) those in which the resistance of the erythrocytes is diminished. He concluded that changes in the constitution of the blood cells and hence, their resistance, might occur as a result of any one of a variety of etiological factors—syphilis, malaria, inanition, infectious disease, suppurative process, neoplasm.

Such was the conception of the disease at the time that the studies of Donath and Landsteiner (1904) illuminated the underlying mechanism

of the disease and demonstrated a test tube paradigm of what apparently is the essential feature of the disease. These Viennese immunologists, using oxalated blood from the finger, observed that in a mixture of the patient's plasma and red blood cells left in ice water for a half hour no hemolysis occurred from the chilling alone, but that when the mixture was warmed the supernatant liquid became colored with hemoglobin. Subjecting this reaction to further experimental analysis they demonstrated (*a*) that the serum or plasma of these patients contains a lysin having the peculiar characteristic of being capable of uniting with the red cells only at low temperatures, (*b*) that the hemolytic reaction takes place in two phases—first, union of lysin and red cell at the low temperature and then, after the mixture is warmed, lysis of the red cells, (*c*) that complement (alexin) is essential for the second phase of the reaction, (*d*) that the lysin is both an autohemolysin and an iso-hemolysin, (*e*) that the red cells of these patients are not hemolysed by the serum of normal individuals. This work stimulated many to study the serological reactions of these patients; abundant confirmation (Widal and Rostaine, Langstein, Eason, Grafe and Müller) of the Vienna observations was promptly forthcoming and the characteristic reaction is now almost universally known as the Donath and Landsteiner, or as the Landsteiner reaction. Occasionally in publications from Great Britain it is referred to as the "Eason phenomenon," because in 1906 Eason described the same effects from chilling mixtures of red cells, serum and complement. He stated that his original communication was made before the Galenian Society of Edinburg in January, 1904, and since the first published description of the reaction by Donath and Landsteiner appeared in September, 1904, Eason claimed priority. A search of the literature, however, fails to reveal any published record of such a communication before the Galenian Society.

Since 1904 many studies of the serological mechanism of the disease have been published. The more accurate diagnosis of syphilis by means of the Wassermann reaction (1906) made it clear that certainly nearly all and probably all genuine examples of paroxysmal hemoglobinuria are the result of syphilis; additional information has been gained about the behavior of the lysin; the clinical manifestations of the disease have been more thoroughly studied and the effects to be

expected from various forms of treatment are better known. In brief, the twenty-five years since the first publication of Donath and Landsteiner have witnessed the addition of many details to our knowledge of the disease, but very little of fundamental significance. Donath and Landsteiner believed that the characteristic serological reaction discovered by them was an adequate explanation of the *in vivo* mechanism of the disease. A number of observations which will be referred to later have, however, cast a good deal of doubt on the validity of this conclusion. Despite the possibility of modification of their views on this fundamental question, their work stands as the most important single contribution toward comprehension of the mechanism of the disease.

CLINICAL MANIFESTATIONS

The symptomatology of this disease involves not only the clinical events occurring during an attack, but also the more chronic effects of blood loss and almost any of the multifarious effects of late syphilis, either congenital or acquired.

In about 30 per cent of these patients clinical examination reveals unquestionable evidence of syphilis, but with the Wassermann reaction it is possible to demonstrate syphilitic infection in over 90 per cent. A large variety of syphilitic lesions has been reported in patients with paroxysmal hemoglobinuria, notably aortitis, Hutchinson teeth, saddle nose, bowing of the tibiae, interstitial keratitis, hepatitis, tabes, paresis. The large percentage of congenital syphilitics among the reported cases indicates that the congenitally infected individual is more liable to develop hemoglobinuria than those with the acquired disease. Matsuo records the occurrence of the disease in a boy, his sister and two cousins; several authors have reported more than one case in the same family. The disease appears to be relatively common in Japan.

The patient's attention is usually first arrested by the passage of dark red or brownish, or almost black urine, and he seeks advice for "bloody urine." He is apt to state that following an exposure to cold, which may have been surprisingly slight, certain distinct symptoms occurred before the onset of the paroxysm. The interval between chilling and the beginning of symptoms may be only a few

minutes or it may be seven or eight hours. These prodromal symptoms are apt to be aching pains in the back and legs or in the abdomen, abdominal cramps, headache and malaise. Usually the actual paroxysm begins with a severe shaking chill and a subsequent rise of temperature to 102° to 104°F., but cases are on record in which paroxysms occurred without either chill or fever. The period of elevated temperature may be brief or may continue for several hours. In the typical attack the first urine passed following the chill is highly colored. It may be a dark Burgundy red or brownish chocolate color or almost black, depending upon the relative amounts of oxyhemoglobin, methemoglobin and hematin present. Many patients excrete grossly visible quantities of blood pigment only in the first or in the first two specimens passed after the chill, but cases have been reported in which the hemoglobinuria has continued for two or three days. Namba has observed the excretion of rose-colored urine following spontaneous paroxysms or cold foot baths. Chemical and spectroscopic examination of such urine showed that it contained instead of hemoglobin, a pigment known as uroerythrin, presumably derived from hemoglobin. The erythrin could be demonstrated only in patients whose serum contained the Donath-Landsteiner hemolysin. Following the more severe attacks of hemoglobinuria a little icteric staining of the sclerae and skin is perceptible for a few days. During a paroxysm enlargement of the spleen is not uncommon. Less frequently a transitory enlargement of the liver is also demonstrable.

These patients show a very wide range of variability in the amount of chilling necessary to bring on an attack. Macalister found that 40°F. was the effective temperature in one patient. The patient of Bristowe and Copeman would have an attack if exposed to 51°F. The patient of Strominger and Gottfried was susceptible to attacks from such slight chilling as opening the door from an unheated room. One patient observed by the writer had numerous spontaneous attacks while in bed in a well heated hospital ward, and was seen in an attack in the middle of July in New York City. He was a typical example of the disease, a congenital syphilitic, aged 7, with Wassermann and Donath-Landsteiner reactions positive and Raynaud's syndrome. Kumagai and Namba have also seen a case with attacks during the summer. Their patient had the highest titer of autohemolysin they

had observed. Grafe has recorded a similar case. Nearly all paroxysmal hemoglobinurics have attacks when the hands or feet are immersed in ice water for ten to twenty minutes, and this artificial production of attacks (Rosenbach test) is therefore useful in diagnosis. The degree and duration of the chilling necessary to produce an attack artificially are, like the chilling required to bring on spontaneous attacks, highly variable. Eating large amounts of ice failed to cause attacks in the patient of Luzzati and Sorgente even though this patient was extremely susceptible to paroxysms from chilling of the external surface of the body. The patient of Roch and Liengme did, however, have paroxysms after cold drinks. Boas had found that inhalation of very cold air would not produce an attack. Venous stasis by means of a tourniquet has been shown capable of inducing hemoglobinaemia in some of these patients. The writer has tried this unsuccessfully in three patients. Exertion without chilling appears capable in some paroxysmal hemoglobinurics of bringing on attacks (Prior, Connors, Kumagi and Namba). The significance of such cases from the viewpoint of the mechanism of the disease will be discussed later. The case reported by Fleischer (1881) has been considered an early example of the production of a paroxysm by exercise rather than chilling. This patient, however, was probably an example of *Marschhämoglobinurie* and not paroxysmal hemoglobinuria. There was no suggestion of syphilis (except the dubious evidence of inequality of the pupils), marching brought on attacks, but exposure to low temperatures without walking or marching was without effect. Since this was before the discovery of the Wassermann and the Donath-Landsteiner reactions, certainty is not possible but it seems highly probable that this was the same disease subsequently described by Porges and Strisower, and Schellong—a condition occurring mainly in soldiers, in which hemoglobinaemia and hemoglobinuria occur after marching or even standing in the lordotic position. Other forms of exertion not involving a severely upright posture generally cause no hemoglobinuria. In these patients there is no association with syphilis, no auto-hemolysin in the blood, and no hemolytic effect from chilling.

Whether or not emotional episodes may also incite to activity the hemolytic mechanism of paroxysmal hemoglobinuria is not entirely clear, but in one of the patients observed by the writer, the 7-year

old congenital syphilitic with otherwise typical manifestations of paroxysmal hemoglobinuria referred to above, anger and fear also appeared capable of bringing on attacks. He was so highly sensitive, however, to even very slightly lowered temperatures that some doubt existed as to whether emotional disturbances alone could cause hemoglobinuria. Roch and Liengme record an attack brought on in one patient by the intravenous injection of 5 centigrams of casein.

Spectroscopic examination of the urine passed during paroxysms of this disease has shown that the color of the urine is due to oxyhemoglobin and methemoglobin with, sometimes, hematin also. Specimens examined immediately after they have been passed may show also a few intact red cells. The "ghosts" of erythrocytes are commonly found and may be so abundant as to settle out in a heavy sediment. Albumin is regularly present. Red blood cell casts have frequently been noted. Eason found the urea nitrogen in the urine 99.6 per cent of the total nitrogen during a paroxysm, and on the following day 86.4 per cent; the day before the attack it had been 83.5 per cent of the total nitrogen.

Abortive, rudimentary, frustrated or larval attacks. These descriptive terms have been used for various types of incomplete paroxysms. The occurrence of hemoglobinuria without the constitutional manifestations of fully developed attacks—chill, fever, malaise, headache—has been described by Lichtheim, Prior, Moro and Noda, and others. The converse of this clinical picture has also been frequently noted—typical constitutional symptoms without hemoglobinuria (Luzzati and Sorgenti, Bürger, Kumagai and Inoue, Bondy and Strisower). Such attacks, even though no hemoglobin is detected in the urine, are usually characterized by a transitory albuminuria. Kaznelson speaks of "paroxysmalen Kältikterus" because he observed a patient with the usual constitutional symptoms followed by jaundice but no hemoglobinuria. An increase in the serum bilirubin was demonstrable. Careful questioning of patients subject to fully developed attacks not infrequently reveals evidence of the spontaneous occurrence also of attacks without gross hemoglobinuria; furthermore, in attempts to produce attacks artificially by immersion of the hands or feet in ice water the writer has observed the characteristic sudden drop and subsequent increase of the leucocyte count, chill, tempera-

ture elevation, and rise of blood pressure associated with hemoglobinaemia, but no hemoglobinuria. A transitory albuminuria regularly occurred, however, in these abortive paroxysms. Bristowe and Copeman have used the terms "petit mal of hemoglobinuria" for these abortive episodes in paroxysmal hemoglobinuria. Pribram has described a "frustrated attack" in which there was a chill and fever but neither hemoglobinaemia nor hemoglobinuria; it occurred at a time when he found the cholesterin content of the blood increased and the Donath-Landsteiner reaction negative; at another time when the blood cholesterin was low a fully developed attack occurred and the Donath-Landsteiner reaction was positive. The inference was drawn that low blood cholesterin increased the susceptibility to paroxysms. Burmeister, on the other hand, was unable to confirm the observation that the occurrence of attacks was related to the cholesterin or lecithin content of the serum or red blood cells. It is clear from the observations referred to that paroxysmal hemoglobinuria patients are subject to incomplete attacks of several types, either from ordinary exposure to low temperatures or as a result of intentionally chilling a portion of the body surface. In this connection the study by Feigl of hemoglobinaemia and hemoglobinuria in soldiers after an army pack march of 35 kilometers is of interest. Of the 27 soldiers on whom observations were made 15 showed by the spectroscopic method hemoglobin or hematin, or both, in the serum; of the same 27 subjects 19 showed by chemical methods the presence of oxyhemoglobin, methemoglobin or hematin in the urine. Erythrocytes were found in the urine of 8 of the 27 soldiers.

Vasomoter phenomena. Many authors have recorded the occurrence of vasomotor disturbances of one sort or another in association with paroxysms of hemoglobinuria. One of Moss' cases, prior to the onset of attacks of hemoglobinuria, was subject to outbreaks of hives on the face and body after exposure to cold. Kumagai and Namba noted frequent vasomotor phenomena in the 14 cases studied by them. These disturbances may occur in the interval between the chilling and the onset of the chill or they may occur during the actual paroxysm. Raynaud's syndrome is one of the commonest occurrences. Fingers or toes, the tip of the nose, the lips or the ears may be blanched or become deeply cyanotic. Symptoms of this type occurred in 2 of the 5 patients I have observed. Urticarial wheals are not uncommon.

Orel observed the disease in twins. Both children had small white vesicles on the face when exposed to the cold. These disappeared when the children were put in a warm place. The marked changes in systolic and diastolic blood pressure which may occur before the beginning of the chill (Meyer and Emmerich) are presumably also dependent upon vasomotor disturbance. It seems probable, for reasons to be advanced later, that the vasomotor system may be involved in the mechanism responsible for the hemolysis.

SEROLOGICAL MECHANISM

Before the studies of Donath and Landsteiner only the vaguest notions of the mechanism of paroxysmal hemoglobinuria existed. That there was an intravascular hemolysis was generally accepted, but whether this was dependent upon abnormal fragility of the erythrocytes, or upon the liberation under the influence of cold of a hemolytic ferment of endothelial origin (Ehrlich), or upon the presence in the blood of a hemolysin was quite unknown. The original paper of Donath and Landsteiner describes studies made on 3 cases. Using oxalated blood from the finger they mixed 15 drops of plasma with 5 drops of a heavy suspension of erythrocytes, placed the mixture in ice water for $\frac{1}{2}$ hour and then in the incubator for 2 hours and found the supernatant plasma colored with hemoglobin. Normal blood treated in the same way failed to show hemolysis; but the erythrocytes from a normal individual mixed with the serum of a paroxysmal hemoglobinuria patient behaved in the same way as the erythrocytes from a patient, while normal serum and erythrocytes from a patient failed to show hemolysis. The significant factor was thus shown to be in the patient's serum. Inactivation of the serum by heat prevented the occurrence of hemolysis, but the addition of fresh complement to a mixture of inactivated serum and erythrocytes resulted in hemolysis when the mixture was chilled and warmed. The reaction was therefore demonstrated to be an example of an antigen-amboceptor-complement mechanism with the surprising peculiarity that the amboceptor unites with antigen only at a low temperature. The two phases of the reaction were clearly shown by allowing the erythrocytes to absorb the lysin in the cold, removing the supernatant fluid, adding it to other erythrocytes, chilling and warming this mixture, and observing no hemolysis. The two phases were in this way shown to be

(1) absorption of the lysin by the erythrocytes in the cold, (2) lysis of the sensitized erythrocytes at a higher temperature if complement is present. Subsequent studies (Yorke and Macfie) have shown that chilling for 5 to 7 minutes results in greater hemolysis than chilling for 30 minutes. This feature of the Donath-Landsteiner phenomenon, like the union of lysin and erythrocytes only at a low temperature, is somewhat paradoxical. It has been suggested that it is dependent upon degradation of the lysin after long exposure to the low temperature, rather than upon the distribution of complement mid-piece among more and more cells the longer chilling is continued, until a point is reached at which the cells contain such a small amount of mid-piece that it is ineffective when combination with end-piece takes place (Yorke and Macfie). Moro and Noda found that hemolysis occurs very promptly after the serum-erythrocyte-complement mixture is warmed; even after one minute at the incubator temperature hemolysis has occurred. That the union of the lysin and erythrocytes does not always require the temperature of ice water has been shown in a number of instances. In a case studied by Grafe union occurred at 20°C.; this patient was subject to spontaneous attacks at relatively high temperatures and there was therefore a close parallelism between the conditions necessary for the *in vitro* and *in vivo* reactions. Moro and Noda observed evidence of union at 17°C., and Donath and Landsteiner once found slight hemolysis after the lysin and erythrocytes had been exposed to about 20°C.; in 2 other cases studied by them union occurred at 10° and 15°C. respectively. With a 1:1 mixture of serum and 1 per cent erythrocyte suspension Yorke and Macfie observed union at 10°C. and possibly a little union at 15°C. The highest temperatures at which union could be detected (using a 5 per cent erythrocyte suspension) in three patients studied by the writer were respectively 10°, 12° and 10°C. With the lysins from these patients, however, temperatures down to 4° or 5°C. gave more complete union—as shown by greater hemolysis when the mixture was subsequently warmed. These determinations of the highest temperatures at which union will take place between lysin and erythrocytes will vary somewhat according to the concentration of the erythrocyte suspension used. Using fixed amounts of lysin and complement and varying concentrations of erythrocyte suspensions it will be observed that hemolysis may occur

with heavy suspensions when it is entirely absent in the tubes containing light suspensions (Donath and Landsteiner, G. M. Mackenzie).

That complement or alexin is an essential component of the mixture in the Donath-Landsteiner reactions has been verified by everyone who has carefully studied the blood of these patients. A mixture of inactivated serum and erythrocytes chilled and warmed yields no hemolysis, but inactivated serum + erythrocytes + complement treated in the same way gives hemolysis if the lysin is present in the serum. This experiment may, however, fail if inactivation is done at the usual temperature (56°C.). With serum from one of the writer's patients 45°C. for 30 minutes destroyed the lysin so that addition of complement failed to reactivate it; with serum from another patient 47.5°C. for 30 minutes destroyed it. With such extremely thermolabile lysins one will fail to demonstrate the presence of lysin if the serum has been inactivated at 56°C. for 30 minutes. Furthermore, the thermolability of the lysin has been observed (Yorke and Macfie) to fluctuate from time to time. A positive test is in many instances obtained simply by chilling and then warming the patient's whole blood, but owing to the low titer of complement frequently present in human blood, a negative test may be obtained by this procedure when a positive result would have been obtained if fresh guinea pig complement had been added. Meyer and Emmerich have nevertheless reported that even in the absence of complement from the patient's serum, spontaneous attacks may occur from exposure to cold.

Most of those who have studied the blood of these patients have concluded that complement does not participate in the first phase of the reaction, the phase of union of lysin with the erythrocytes. Moss, on the contrary, reported observations which he interpreted as showing that the union of lysin and erythrocytes takes place only in the presence of complement. Numerous observations on the absorption in the cold of inactivated lysin by erythrocytes are opposed to this conclusion of Moss. Using quantitative methods the writer has observed, however, that hemolysis is greater if complement is present throughout both phases of the reaction, then when it is added after the lysin-erythrocyte mixture has been warmed to 37°C. But such results may well be due to the increase of complement activity which with some sera results from chilling (Cooke). Hoover and Stone,

Gilbert, Chabral and Bénard, and Dennie and Robertson also have found that complement is necessary at the low temperature, holding that only at the low temperature does complement become fixed. Widal, Abrami and Brissaud conclude from their studies that complement may fix at the low temperature, but that it is not indispensable until the mixture is warmed. The studies of Meyer and Emmerich, Kumagai and Namba, and Kumagai and Inoue have helped to explain the occasional failure to obtain a positive Donath-Landsteiner reaction in otherwise typical cases. Using quantitative methods for determining the lysin content of the serum of their patients they observed that with repeated attacks the complement in the patient's serum disappears and the addition of fresh complement is then necessary in order to obtain a positive reaction (cf. also Jedlicka, and Meyer and Emmerich). If the attacks are still more frequent not only is there no demonstrable complement, but the serum becomes anti-complementary. To obtain a positive reaction with such a serum it is necessary to wash the sensitized erythrocytes with cold physiological salt solution, then add complement and warm the mixture. Even though it is not always essential that complement be present during the first phase of the Donath-Landsteiner reaction, it is absorbed by the lysin-corpuscle complex if it is present during the chilling process. Meyer and Emmerich demonstrated that complement may be absent from the serum of paroxysmal hemoglobinuria patients following an attack, not only by the negative result of the Donath-Landsteiner reaction, but also by the failure of the patient's serum taken at this time to activate a sheep blood-immune rabbit serum system which at other times it did activate. They also made the interesting observation that in the Ehrlich test complement is apparently formed locally. It was present in the serum from a finger subjected to venous stasis and chilling, but not present in the serum from another finger which had not been tourniqueted and chilled. Cooke showed that during the *in vitro* chilling process both lysin and complement are removed from the serum. Donath and Landsteiner had shown that no complement is absorbed if lysin and complement are added to erythrocytes at body temperature.

Emile-Weil and Stieffel call attention to the fact that sometimes hemolysis results if one removes the supernatant serum from a chilled mixture of lysin-containing serum and erythrocytes and then adds

sodium chloride instead of fresh complement. Hemolysis after such a procedure is not surprising, however, in view of the evidence that complement as well as lysin may fix at the low temperature.

The discrepancies reported by different workers on the nature and behavior of complement in paroxysmal hemoglobinuria are probably to be explained, first by the lack of uniformity in the characteristics (thermolability, temperature required for fixation, titer) of the lysin from different patients and by the complex nature of complement. Ferrata found that complement can be split into mid-piece and end-piece, and Neufeld and Händel, and Sachs and Bolkowska, using the sheep blood-immune rabbit serum system, demonstrated that complement, especially the mid-piece can fix at 0°C., sometimes also the end-piece. Kumagai and Ito, in attempting to analyze the behavior of complement in paroxysmal hemoglobinuria, found that the mid-piece of this hemolytic system requires a low temperature for fixation, and that the end-piece does not. They, as well as Coca and Cooke, found that the complement of paroxysmal hemoglobinuria is different from the complement of sheep blood-immune rabbit serum hemolysis. In one respect, however, the results of Kumagai and Ito are at variance with those of most other workers except Moss. From their experiments they conclude that complement must be present during the first phase of the reaction, but beginning with Donath and Landsteiner (1908) many observations have been made on the occurrence of hemolysis when complement was added only after the inactivated serum-erythrocyte mixture had been chilled and warmed (cf. also Gilbert, Chabrol and Bénard). Kumagai and Ito also obtained evidence of the presence of the so-called third component of complement in paroxysmal hemoglobinuria serum.

The behavior of complement in the Donath-Landsteiner reaction appears therefore to be: complement is essential for the completion of the hemolytic process; it need not be present at the low temperature, but causes greater hemolysis if it is present throughout the reaction; if it is present at the low temperature it (mid-piece) is absorbed by the lysin-erythrocyte complex, and also absorbed in most cases, if added after the lysin-erythrocyte complex has been warmed to 37°C. Some of the failures to obtain positive Donath-Landsteiner reactions in patients having otherwise typical manifestations of the disease have

been due to the absence of complement or to anticomplementary properties in the patients' serum, conditions apt to occur after attacks.

The evidence for fluctuations in the titer of the autohemolysin is much less convincing. The difficulties of performing an accurate titration with a labile lysin are obvious, and most investigators of this disease have not used quantitative methods. Those who have observed different amounts of hemolysis (Moro and Noda, Jamada, Matsuo) with the serum of the same patient taken at different times have not excluded the possibility of the variations being due to fluctuations in the complement or to anti-complementary action. Kumagai and Namba have found that if one takes the necessary precautions to prevent weak complement activity or anti-complementary action of the serum interfering with the lysin titration, the titer of a patient's lysin fluctuates very little. There is, however, a trend downward in the titer under anti-luetic treatment. The writer has observed one patient the titer of whose lysin declined for two years while receiving anti-syphilitic treatment, and then for two years, when he received only a small amount of treatment, it remained at the same titer; it finally disappeared shortly after treatment was resumed. Kumagai and Namba have stated that the severity of the disease parallels the titer of the hemolysin, but this seems not to be an invariable rule. Titrations of the lysin of two boys, both congenital syphilitics, showed an inverse relationship between titer of lysin and susceptibility to attacks (G. M. Mackenzie).

In much of the earlier work no account was taken of the different blood groups[1] and hence some of the early observations on the isolysin of paroxysmal hemoglobinuria are unreliable. But all who have excluded the hemolytic effect of normal isolysins in serological studies of paroxysmal hemoglobinuria have confirmed the original observations of Donath and Landsteiner that the serum of these patients contains an isolysin which fixes in the cold. Sometimes the isohemolytic activity is stronger than the autohemolytic (Meyer and Emmerich) and sometimes the reverse has been found. The isohemolysin has been reported to occur without any demonstrable autohemolysin (Matsuo) and this would suggest that the two functions are represented by different components of the serum, but this work was

[1] Witebsky's three cases all were in Group A. The writer's five cases were distributed as follows: Group 0, 2 cases; Group A, 2 cases; Group B, none; Group AB, 1 case.

done without reference to blood groups. Absorption experiments, however, have failed to provide any evidence that the iso- and auto-hemolysins are different. When one is absorbed the other disappears at the same time and to the same extent (Lorant, G. M. Mackenzie). The isolysin here referred to is not to be confused with the normal iso-hemolysin sometimes present in human serum for erythrocytes of different blood groups. The isolysin discussed above is shown by the capacity of the serum of paroxysmal hemoglobinuria patients to hemolyse by the chilling test the blood cells of other individuals in the same blood group.

A titration of the lysin content of the supernatant serum from a chilled mixture of inactivated lysin and a heavy suspension of erythrocytes compared with the lysin content of the supernatant serum of a similar mixture, which has been both chilled and incubated at 37°C. shows that incubation after chilling causes a certain amount of dissociation of the lysin; the supernatant serum from the mixture which has been incubated after chilling has a higher titer of lysin than the supernatant serum from the mixture which has been chilled and centrifugalized cold (Meyer and Emmerich ,Browning and Watson, Cooke). Cooke found that when 90 per cent of the lysin had been absorbed in the cold, 25 per cent was dissociated during 30 minutes at 37°C. From these observations on dissociation at 37°C. it is obvious that the lysin-erythrocyte union is a labile one. The experiments of Yorke and Macfie showed that when complement is present at the low temperature the lysin is not "disgorged" at 37°C., and also that no mid-piece is dissociated. Since it is chiefly, if not exclusively mid-piece of complement which fixes at the low temperature, the evidence indicates that the lysin-erythrocyte-mid-piece combination is more stable than the lysin-erythrocyte complex.

An as yet unexplained discrepancy exists in the matter of a possible activating effect by CO_2 on the hemolytic mechanism of this disease. Prior to the experiment of Hijmans van den Bergh assumptions had been made (Chvostek, Murri) that CO_2 might play a rôle in the mechanism of the disease. Mannaberg and Donath had indeed passed CO_2 through the blood of a paroxysmal hemoglobinuria patient and observed hemolysis, but attached no significance to it because they found hemolysis also when normal blood was treated in the same way. Hijmans van den Bergh found that defibrinated

paroxysmal hemoglobinuria blood exposed to CO_2 at room temperature (16°C.) behaved as though it had been chilled and warmed—i.e., there was hemolysis. The same blood did not hemolyse when exposed to room temperature without CO_2 nor when it was exposed to CO_2 only at 37°C. Normal erythrocytes mixed with paroxysmal hemoglobinuria serum and exposed to CO_2 at 16° were hemolysed. Addition of complement was found unnecessary. Inactivated lysin-containing serum could not be reactivated for the CO_2 hemolysis by the addition of fresh complement. Normal blood did not hemolyse under the conditions of these CO_2 experiments. These results have been confirmed by Hannema and Rytma. It is not clear from these experiments, however, whether CO_2 acts simply as an activating factor for the Donath-Landsteiner mechanism or whether it represents a distinct and separate hemolytic mechanism—the evidence points more to the latter assumption. No experiment was done to determine whether the CO_2 hemolysis would occur after removal by absorption of the Donath-Landsteiner lysin; the experiments were not done with quantitative methods nor is the concentration of CO_2 reported. Kumagai and Ito studied this phenomenon and failed to confirm the findings of the Dutch investigators. They performed the absorption experiment and found that CO_2 hemolysis disappeared with the absorption of the Donath-Landsteiner lysin. In their experiments the hemolysis occurred at 16° both in the air and in CO_2. They found the CO_2 hemolysis in 4 cases uncertain and irregular, and believe the supposed effect of CO_2 is simply due to the Donath-Landsteiner mechanism which will sometimes act at 16°C. The writer has also tried without success to confirm the observations of Hijmans van den Bergh. This problem of CO_2 hemolysis needs further investigation before definite conclusions can be drawn. From both theoretical and practical viewpoints it is important to know if CO_2 is the additional factor involved in the paroxysmal hemoglobinuria mechanism. Such a factor has been postulated repeatedly from evidence of several kinds. The occasional patient, fulfilling the other criteria of this disease, who has paroxysms of hemoglobinuria from exertion or during warm weather suggests that actual chilling is not always necessary. So, too, observations which indicate that the degree of susceptibility to attacks does not always run parallel with the titer of the hemolysin

make probable the participation of some factor in addition to the demonstrated components of the Donath-Landsteiner mechanism. On clinical grounds the disturbances of the vasomotor apparatus have been suspected of playing a rôle, but whether these are dependent in any way upon CO_2 is by no means clear from the evidence available. In appraising the validity or significance of investigations of the serological mechanism of this disease it should be borne in mind that the properties of the lysin from different patients have been shown to manifest considerable variations: its thermolability is by no means the same in all patients, nor in the same patient at different times, nor is the highest temperature at which it will unite with erythrocytes a constant, nor its relative avidity as an auto- and iso-lysin; and perhaps the same is true of the necessity of complement being present during the first phase of the reaction.[2]

[2] The description of the mechanism of this disease as set forth in the preceding pages is almost universally accepted and has seemed to most of those who have studied the disease, to explain the known facts. However, an alternative conception of the mechanism was offered by Widal and his collaborators soon after the original studies of Donath and Landsteiner were published. On the basis of experiments in which it was found that the serum of a rabbit immunised either with human serum or with the serum of a hemoglobinuric would inhibit the Donath-Landsteiner reaction, the French investigators postulated a mechanism dependent upon deficiency of anti-sensibilisatrice (antilysin) in the blood of hemoglobinurics. Normal individuals, they said, have in their serum a sensibilisatrice (lysin) and an anti-sensibilisatrice (anti-lysin) in a state of stable equilibrium. In the blood of the hemoglobinuric this equilibrium is labile. As a result of chilling there occurs a dissociation of lysin and anti-lysin with fixation of the dissociated lysin and complement by the erythrocytes; hemolysis occurs when this complex is warmed. The original features of this conception consist of (*a*) the existence of the lysin in normal individuals, (*b*) the existence of an anti-lysin in normals and hemoglobinurics. Even if anti-human rabbit serum does inhibit the Donath-Landsteiner reaction, this is scant evidence for the assumption of an anti-lysin. Such an immune serum as Widal employed would precipitate the serum proteins of human serum, either hemoglobinuric or normal, and precipitation would be expected to carry down in the precipitate any lysin present and thus prevent union of lysin and erythrocyte. To assume the existence of anti-lysin therefore seems unwarranted.

Salén in a voluminous contribution to the subject of paroxysmal hemoglobinuria has offered a conception of the mechanism of the disease differing from that set forth in this review and from that of Widal. His theory is that, as a result of chilling, a part of the dispersed colloid constituents of the plasma, probably the globulin, undergoes a change in its physical state; that as a result of this physical change the plasma acquires the power of so altering the erythrocytes that they behave like sensitized cells; that if lytic properties are present in the plasma the sensitized cells, or a certain portion of them, are hemolysed. Much of Salén's paper is taken up with vague discussions of various aspects of the disease from the point of view of his theory, and seems to the writer unsuitable for critical review. For the details of this conception the original should be consulted.

PATHOGENESIS

Relation to syphilis

Early observers of the disease, as has been stated, suspected that syphilis was the chief, if not the sole etiological factor in paroxysmal hemoglobinuria (Murri). The frequency of the disease in congenitally syphilitic children and lesions of acquired syphilis in many of the adult patients pointed clearly in this direction. The more exact criteria for the diagnosis of syphilis afforded by the Wassermann reaction confirmed the earlier clinical conclusions, and it was soon evident (Meyer and Emmerich, Matsuo, Kumagai and Ito, Browning and Watson) that in over 90 per cent of patients with paroxysmal hemoglobinuria the Wassermann reaction is positive, a figure not far from that obtained in patients known to have syphilis. A review of the literature between 1906 and 1925 (Donath and Landsteiner) showed that of 99 cases reported there was evidence of syphilis in 95. Of these there was a positive Wassermann reaction in 81 and a history or clinical evidence of syphilis in 24. All of the 5 cases studied by the writer showed positive Wassermann reactions; in two of them the Wassermann titer was exceptionally high, but there was no distinct parallelism in the titers of the auto-hemolysin and the Wassermann reacting substance. In their early studies of the disease Donath and Landsteiner examined the blood of 93 patients with general paralysis for the presence of the characteristic auto-hemolysin. Only one of these patients had symptoms of paroxysmal hemoglobinuria. The hemolysin was demonstrable in 7 individuals of this group. In two of them a positive Ehrlich test was obtained. In one patient general paralysis and paroxysmal hemoglobinuria coexisted. Confirmation of these results has come from Kumagai and Namba who studied 35 patients with late syphilis and found the auto-hemolysin present in 7. The Ehrlich test was positive in all 7. In one of these patients a cold foot bath produced a typical attack of hemoglobinuria; in 3 others only albuminuria occurred after immersion of the feet in cold water. The evidence seems, therefore, to justify the conclusions (1) that paroxysmal hemoglobinuria is usually and perhaps always a manifestation of syphilis and (2) that a small percentage of patients with late syphilis have the latent form of paroxysmal hemoglobinuria. In this connec-

tion, however, Burmeister's results and conclusions should be mentioned. In 207 cases in the literature he found indications of syphilis in only 79; in 43 it was ruled out; in 1 it was uncertain, and in the remainder there was no information as to the presence or absence of syphilis. Nevertheless, he found that the Wassermann reaction was positive in 95 per cent of the cases in which it was reported. He also described experiments in which he absorbed the auto-hemolysin in the cold by means of erythrocytes and found that not only the lysin but also the Wassermann reacting substance had disappeared. This result is quite contrary to the findings of Moro and Noda, R. P. Smith, Yamada, Matsuo and Kaznelson. The writer has repeatedly performed this experiment and without exception has found that the Wassermann reacting substance not only does not disappear, but shows no significant change in titer as a result of removal of the lysin. Burmeister also found that when he dissociated the lysin from sensitized erythrocytes that the fluid so obtained gave a positive Wassermann reaction. He concludes that in some cases paroxysmal hemoglobinuria occurs without syphilis—even though the Wassermann reaction is positive—and in other cases that there is a relationship between the two diseases. In this latter group he believes that the auto-hemolysin and the Wassermann reagin are the same. Burmeister's experimental results and his conclusions in regard to the relation of syphilis to paroxysmal hemoglobinuria are so different from those of other workers that confirmatory experiments are needed to justify acceptance of his ideas.

A number of those (Meyer and Emmerich, Moss, Rosin, Foix and Salin, Salén) who have studied paroxysmal hemoglobinuria have considered the question of why during the course of a syphilitic infection the infected individual should develop an antibody for his own erythrocytes. Presumably the lysin is formed as a result of immunological processes, but it can hardly be due simply to auto-immunization to antigens of erythrocytes destroyed within the body, for no such lysin develops in other conditions in which blood destruction occurs—for example, malaria, black water fever (Barratt and Yorke), hemolytic icterus, internal hemorrhage, and after the therapeutic procedure of subcutaneous injections of an individual's own blood. It is necessary to postulate some other mechanism or some additional factor.

Perhaps a clue to the mode of origin of the auto-hemolysin is provided by the experiments of Namba. He found that when rabbits, either syphilitic or non-syphilitic, are injected intraperitoneally with organ emulsions such as guinea pig kidney, or liver, heart, kidney, brain, spleen or lung of dog, horse, calf, hog or rabbit, an auto-hemolysin is developed which requires complement and unites with the erythrocytes only in the cold. Kidney emulsions were found most effective in the production of these auto-hemolysins in rabbits. That he was not dealing with the Forssman antigen may be inferred from the fact, which he points out, that calf kidney contains no Forssman antigen but produces the auto-hemolysin. In rabbits prepared with such emulsions he produced hemoglobinaemia by putting an elastic band around an ear and immersing it in ice water. The reported production of a positive Wassermann reaction by injection of rabbits with organ emulsions is interesting in relation to the observations of Namba. The facts therefore point to the conclusion that syphilitic infection involves the liberation of antigens either from the spirochaetes themselves or from the organs of the host or from both, which determine the production by the infected individual of antibodies of more than one type—i.e., the auto-hemolysin and the Wassermann reagin. Since the evidence indicates that these substances are not identical one must assume that antigens of more than one kind are released by visceral syphilis, and that the lysin is produced in response to the liberation of antigens of visceral or spirochaetal origin rather than of erythrocyte origin. Why some syphilitics develop the auto-hemolysin and others do not is quite obscure.

Relation of the auto-hemolysin to the occurrence of attacks

Several considerations have led to the belief that the Donath-Landsteiner reaction is a reproduction *in vitro* of what actually occurs in the vascular system of a patient when he has an attack of hemoglobinuria. The *in vitro* and the *in vivo* reactions are both dependent on chilling; in harmony with the demonstration that the *in vitro* reaction is more complete with short chilling is the obvious fact that erythrocytes in superficial capillaries can be exposed to a low temperature only for a short time before passing to the higher temperatures of the interior of the body; union of the lysin and erythrocytes

may occur at temperatures as high as 16° to 20°C. and it seems quite possible that blood in superficial capillaries might be exposed to such temperatures; furthermore the heavy suspension of erythrocytes existing in whole blood is more favorable for the occurrence of hemolysis than lighter suspensions. On the other hand a number of considerations have led some investigators to postulate an additional factor in the hemolytic mechanism of this disease, even though they admit that the essential and specific factor of the mechanism is the lysin. The lysin has been repeatedly demonstrated in the serum of syphilitics free from manifestations of paroxysmal hemoglobinuria; some patients have typical attacks without chilling; there appears to be no strict parallelism between the susceptibility of the patient to attacks and the titer of his lysin. It has been stated that in certain patients attacks may occur with no demonstrable lysin in the serum, but the studies of Kumagai and Namba on the disappearance of complement and the occurrence of anticomplementary properties in the patient's blood following attacks make it highly probable that failure to demonstrate the lysin in otherwise typical cases is due to inadequate technique. Donath and Landsteiner (1925) reported that of 103 cases collected from the literature the lysin was demonstrated in 95; in the 8 other cases the reaction was reported to be negative. They are inclined to think that in testing the blood of the negative cases the more recently discovered technical requirements were not fully complied with, or that failure to obtain a positive result was due to the fact that the test was not repeated. They believe that lysin may fluctuate or even temporarily disappear. This has not been the experience of the writer. Except for a downward trend during antiluetic treatment, the titers of the lysins of 5 cases remained remarkably constant for periods of 2 to 6 years; the rapidity of the fall in titer was roughly proportional to the intensity of the treatment. Kumagai and Namba conclude from their work, already referred to, that the severity of the disease is determined by the titer of the lysin and that the apparent discrepancies to this general rule are due either to failure to provide complement or to anticomplementary properties in the patient's serum. The observations of Hijmans van den Bergh on the supposed participation of CO_2 in the hemolytic mechanism have already been discussed. In view of the failure of Kumagai and Ito

and Mackenzie to confirm the results of Hijmans van den Bergh, acceptance of CO_2 as the additional factor in the hemolytic mechanism should, for the present at least, be conditional.

PATHOLOGICAL PHYSIOLOGY

Pigment Metabolism

An illuminating study of pigment metabolism in paroxysmal hemoglobinuria was made by Jones. Following a typical attack he found that the liberated hemoglobin is rapidly converted into bilirubin. No response was observed in the excretion of bile pigments until all of the hemoglobin and most of the bilirubin had disappeared from the plasma. Subsequently the liver responded to the excess of pigment in the circulation by a marked increase in the output of bilirubin, an excess shown by a quantity in the circulation three times the normal concentration. The accompanying rise in the urobilin and urobilinogen in the bile occurred so close to the peak of the bilirubin curve that the possibility of intestinal formation of the urobilin and urobilinogen was precluded. One may conclude from this work that under the conditions of the observations urobilin is formed in the liver from bilirubin which is formed from hemoglobin. Jones and Jones also demonstrated in a paroxysmal hemoglobinuria patient the extrahepatic formation of bilirubin; they showed that it was present in the blood peripheral to a ligature after the ligatured arm had been immersed in cold water.

The experiments of Sellards and Minot indicate that during a paroxysm of hemoglobinuria it is not the liberated hemoglobin which is responsible for the chill, rise of temperature and other symptoms associated with an attack. They injected intramuscularly or intravenously the hemoglobin obtained by taking amounts of blood varying from 4 to 33 cc. No toxic symptoms were observed. This would suggest that the stroma of the erythrocytes may be responsible for some of the symptoms. Penfold and Robertson, however, produced intravascular hemolysis in healthy rabbits by injections of distilled water without causing fever, even though the hemoglobinuria was marked.

Hematology

Nearly all patients with paroxysmal hemoglobinuria have either a moderate or severe anemia during the period of the year when attacks occur. The severity of the anemia obviously is dependent upon the frequency and severity of the attacks. It has been estimated that the renal threshold for hemoglobin excretion is not overstepped unless at least 60 cc. of blood has been hemolyzed (Ponfick), but there are very few observations on this point. Intravascular hemolysis of small quantities of blood results only in some form of larval attack. The amount of blood which may be hemolysed during a severe paroxysm must, judging from the changes in red blood cell counts and hemoglobin percentage, be very large. Kobler and Obermeyer observed a patient whose red blood cells fell 690,000 per cubic millimeter during an attack; more striking still are the figures reported by Montagnani. Before and after an artificially produced attack he obtained the following counts:

	BEFORE ATTACK	AFTER ATTACK
Red blood cells	3,800,000	1,800,000
White blood cells	8,750	10,800
Neutrophiles	62.6	68
Eosinophiles	2	2.5
Basophiles	0.5	1
Large mononuclears	9	8.5
Intermediate	12	9
Lymphocytes	11	11
Hemoglobin	48	28

Donath and Landsteiner (1925) record a case in which a paroxysm reduced the erythrocytes from 4,300,000 to 3,200,000 and the hemoglobin from 85 to 55 per cent. Luzzatti and Sorgente found in one patient during the summer 5,000,000 red blood cells and 80 per cent hemoglobin; in winter, after repeated attacks, 2,700,000 red blood cells and 35 per cent hemoglobin.

Mannaberg and Donath and others record extremely rapid regeneration in the red cell count and hemoglobin percentage following a paroxysm. In one instance the red blood cells were 895,000 and the hemoglobin 45 per cent. The first day after the attack the figures

were, red blood cells 1,500,000, hemoglobin 45 per cent; the second day, red blood cells 3,500,000; two weeks later, red blood cells, 4,390,000 and hemoglobin 60 per cent. After a paroxysm anisocytosis and poikilocytosis are often present, and basophilic stippling, polychromatophilia, nucleated red cells and myelocytes have been observed (Donath, Grafe and Müller, Meyer and Emmerich, Weinberg). Between paroxysms the total leucocyte count and the differential may show no significant deviations from the normal or, as Meyer and Emmerich have observed, a moderate lymphocytosis.[3] Marked and interesting changes in the leucocyte count occur during a paroxysm. Widal, Abrami and Brissaud observed the sudden decrease of leucocytes which occurs soon after the chilling. This with the accompanying phenomena (increased coagulation time, increased viscosity, fall in blood pressure) they called the hemoclastic crisis and have observed it in a variety of conditions. In an artificially produced attack Montagnani found a fall in systolic blood pressure (115 mm. Hg. to 95), a marked leucopenia (9,800 to 1,000), a decrease in the number of platelets (160,000 to 35,000), increased viscosity, increase of coagulation time and a decrease in the index of refraction. Höglund has reported an increase of platelets from 397,000 to 526,000 $1\frac{3}{4}$ hours after chilling. The writer has studied the changes in the leucocyte picture of three patients during artificially induced attacks. In them the leucopenia was observed to occur as early as 15 minutes after the beginning of the chilling. With the leucopenia there was a transitory relative lymphocytosis, and sometimes following this a leucocytosis with a higher percentage of neutrophiles than was present before the paroxysm. The most exhaustive study of the blood changes during artificial attacks has been made by Uchida. Making leucocyte counts at short intervals he found that there was often a slight initial leucocytosis due to the direct action of the chilling, and that prior to the marked leucocyte drop hemoglobin is always demonstrable in the serum. Within 2 hours of the onset of hemoglobinaemia there is a leucocytosis and relative lymphopenia. He obtained similar blood changes in rabbits after injection of blood derivatives. His conclusion, therefore, that the blood changes in patients during artificially

[3] Lymphocytosis was present in four of the five patients observed by the writer.

induced paroxysms are due to derivatives of hemolyzed erythrocytes, appears to be well founded. Extending the earlier observations of Meyer and Emmerich and those of Gali, Uchida also studied the phagocytosis of erythrocytes by leucocytes in paroxysmal hemoglobinuria. He found in the blood of these patients a substance promoting phagocytosis of the patient's own erythrocytes by his leucocytes; the large mononuclears and the transitionals were most phagocytic, the neutrophiles and the eosinophiles less so. This substance he calls the "auto-hämotropin." It does not act on cells of normal individuals nor on those of other paroxysmal hemoglobinurics. Inactivation of the serum weakens but does not destroy this substance. He also finds an "iso-hämotropin" which is distinct from the "auto-hämotropin," but observed no differences in the "iso-hämotropin" content of normal and paroxysmal hemoglobinuria serums.

THERAPY

The course of this disease without antisyphilitic treatment has been only very meagerly reported in the literature. Browning and Watson reported the case of a boy of 16 who ceased to have attacks and had no recurrence during the two years he was under observation. The lysin, however, was demonstrable in his serum as long as he was observed. Latent cases with the characteristic hemolysin in the serum have been observed to change into fully developed cases, but whether the reverse process also occurs is uncertain. It is clear from the histories of recorded cases that untreated they may continue to have attacks for many years. S. Mackenzie observed a patient who had had attacks for 23 years with no apparent impairment of health. In most instances, however, the patient has come under observation and has either been treated or reported in the literature a few months to a few years after the onset. Numerous forms of therapy have been tried. Sufficient evidence has now accumulated to render all methods except intensive anti-syphilitic therapy of interest only from the viewpoint of medical history.

Widal and Rostaine immunized animals with large doses of human serum. The serum from these immunized animals was used, after inactivation at 55°C., to treat paroxysmal hemoglobinuria patients. They reported a transitory increase of resistance to chilling without

any effect upon the Donath-Landsteiner reaction. Before treatment immersion of the hands in water at 15°C. for 15 minutes caused hemoglobinuria. After two serum treatments, each of 25 cc., immersion of the hands in water at 10°C. for 50 minutes caused neither symptoms nor hemoglobinuria. They thought that the resistance persisted for about 4 weeks. The well known spontaneous fluctuations in susceptibility to chilling of these patients renders the interpretation of Widal and Rostaine of their observations somewhat doubtful. Montagnani tried this method of treatment and found that hemoglobinuria was even more intense after the treatment, and that the phenomena of the hemoclastic crisis still occurred after chilling. He then put the patient on anti-luetic treatment—the hemoclastic crisis no longer occurred, the Ehrlich, Wassermann and Donath-Landsteiner reactions became negative. The patient subsequently, however, had a spontaneous attack.

Grafe and Müller, after a single injection of an antihemolytic immune serum, reported a sequence of events similar to that observed by Widal and co-workers, but they were inclined to attribute the apparent effect to spontaneous fluctuations in susceptibility to cold. Widal, Abrami and Brissaud tried autoserotherapy on 3 patients. They gave 9 to 15 intravenous injections of about 40 cc. of autoserum. They interpreted their results as indicating a transitory protection against attacks. One of their patients was free from attacks for a year. On the basis of observations by Gruber indicating a decrease of complement following injections of normal serum, Glaessner and Pick treated paroxysmal hemoglobinuria by injecting at intervals of about a week, 8 to 10 cc. of normal horse serum. After the second injection they observed an increased tolerance for cold which persisted several weeks, then disappeared, and reappeared after another injection. These authors also found that the lysin remained in the blood during the period of apparent increase of tolerance for chilling, and conclude that the effect of the serum injections was not due solely to fixation of complement.

Bondy and Strisower thought that hypertonic salt solution afforded some protection against attacks, but Kaznelson was unable to confirm this. Salén has used graded cold water foot baths, but others have had only indefinite results by this method. In their series of fourteen

patients Kumagai and Namba tried various methods of treatment—cholesterin, calcium, sodium chloride, peptone, normal human serum, normal horse serum and autoserotherapy. None of these influenced the occurrence of attacks. Then all the patients were given anti-syphilitic treatment. Of the fourteen patients, two were lost to observation, one died, one was still under treatment at the time of writing, and the other ten were clinically cured. Salén's statement that the disease has not been cured by anti-syphilitic treatment is, therefore, no longer valid.

Although numerous authors (Murri, Ehrlich, Götze, Donath and Landsteiner, and others) had previously reported favorable results with anti-syphilitic treatment, the extensive studies of Kumagai and Namba afforded the most convincing evidence of the effectiveness of thorough and prolonged administration of mercury, iodides and arsphenamine. Meyer and Emmerich, to be sure, found anti-syphilitic treatment ineffective, and the results of Matsuo, Salén, Moss, Traub, Young and others have been somewhat equivocal, but in general where anti-syphilitic treatment has failed it has not been carried out with sufficient intensity or for a sufficiently long period. The writer's results on three cases fully corroborate those of Kumagai and Namba. In these three cases it was found that clinical manifestations ceased, the Wassermann reaction became negative and the auto-hemolysin disappeared from the serum in the order named.

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UNDULANT FEVER

Its Relation to New Problems in Bacteriology and Public Health[1]

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It is somewhat hazardous to deliver a formal lecture on a subject in which we are just beginning to realize the importance of accurate data and in which a fair number of questions can be asked and problems formulated, but no definite conclusions drawn. As in nearly all somewhat unexpected developments in science, the new problem of undulant fever in populations not using goat's milk seemed at first simple. The cow was regarded as the source of the infection owing to the wide dissemination of the bovine disease. The problem has grown more obscure and complex with the publication of fresh cases and the more thorough study of the organisms obtainable from them. Hasty conclusions in this as in other fields of public health may do no damage as long as the problem remains in the stage of discussion. The results are more serious when hasty legislation results or new rulings under existing law are promptly invoked. Moreover such action may tend to discourage or stifle further necessary research. In order that the lecture maintain a certain unity I shall view the subject solely from the standpoint of one who is endeavoring to find out from existing data whether or not the bovine type of *Bacillus abortus* produces undulant fever in man, primarily, and not as a secondary invader or graft on some preëxisting pathological state. This formulation of the subject is still sufficiently comprehensive to bring to the surface what is most significant.

There are three known, widely diffused animal sources of the

[1] De Lamar lecture delivered October 30, 1928, before the Johns Hopkins University School of Hygiene.

Brucella group, the cow, the pig, and the goat. In some European countries sheep are hosts. A few horses have been found infected and other host species may be discovered. I assume that the goat and sheep races of *B. melitensis* are the same and that those found in the horse are accidental and aberrant parasites. Hence a brief description of the three major races may well precede a discussion of the human strains.[2]

The bovine disease and its affiliated microbe, *Bacillus abortus*, may be regarded as highly specialized, established types. Both have rather unique characters. In the cow the infectious agent is restricted primarily to the pregnant uterus, more particularly to the fetal membranes (chorion), and secondarily to the udder ducts. There is no clinical disturbance manifested by the pregnant cow and the infected udder presents no signs of mastitis. The special characteristic of the chorionic disease is the invasion of the epithelium by the bacillus and its multiplication therein.[3] In this situation the organism is entitled to be called a Rickettsia. From the chorion the invasion of the epithelial covering passes to the cotyledons and here there develops a gradual blocking of the vascular villi. The fetus suffers not from any localized disease due to *B. abortus* but from a gradual interference with its circulation in contact with the maternal vessels. Death of the fetus is associated with extensive subcutaneous edema, with serous effusions tinged with blood coloring matter into the large serous cavities—conditions referable to a more or less acute interference with the circulation. *B. abortus* may be absent or restricted to the digestive tract of the fetus, or it may very rarely appear in cultures from the viscera. In the cow's udder the bacteria, escaping into it from the circulation, are probably retained in the residual milk from day to day and multiply in it. The calves which drink this milk or which were born at full term in spite of a late uterine infection with *B. abortus* fail

[2] As might be anticipated in a rapidly developing subject, the nomenclature is in a more or less fluid state. The Malta fever organism first described by Bruce in 1889 and subsequently traced to goats was at first named *Micrococcus melitensis*. The bovine organism first isolated by B. Bang in 1897 was called *Bacillus abortus*. The bringing together of these organisms by Alice Evans in 1918 gave impulse to a new terminology. The genus, including pig, goat, and cow strains, became *Brucella* in honor of Bruce, and later another genus designated *Alcaligenes* has been suggested.

[3] Smith, T., J. Exp. Med., 1919, xxix, 451.

to contract any disease probably because there is no pregnant uterus. Very rarely, however, the mucoid fluid of the ducts of the undeveloped udder may harbor *B. abortus*. Such animals will grow up with the udder permanently infected. They may also thereby become immune to the uterine disease and remain as carriers in the herd.

In 1911, M. Fabyan and the writer[4] called attention to a peculiar disease induced in guinea pigs by pathological material containing *B. abortus* as well as by pure cultures of the same. Before this no small animal had been recognized as susceptible to this agent. The study of *B. abortus* was greatly assisted by this new fact, for passage through guinea pigs made it possible, as in tuberculosis, to obtain pure cultures when other methods failed. Since then various species of monkeys have been used by K. F. Meyer and others in attempts to differentiate the bovine from other races of this species. Inoculation of fetal membranes, contents of fetal stomachs and rectum into guinea pigs, or of pure cultures leads to a disease which is non-fatal and self-limited. The infection may be by way of the subcutis or the peritoneal cavity, the dose may be large or small, the condition of the animal, say at the end of eight weeks, is about the same. There is no local lesion or if some swelling occurs it disappears and the subcutis is normal where the material was deposited. The regional and other subcutaneous nodes may be swollen to twice their size or but little. Necrotic foci are absent unless other bacteria were introduced in pathological material. The only other changes are a large, highly congested spleen with dimensions one and one-half to three times the original, with or without numerous minute gray foci, and an infiltration followed by suppuration of the epididymis of one or both testicles. The body of the testicle is not visibly involved. Rarely swelling of the carpal joints is present. Although *B. abortus* may be obtained from most organs if sufficiently large pieces are cultured, with the exception of the abscessed epididymis, the spleen contains the larger number. The bacilli slowly multiply in the guinea pig up to the fourth week and then decline. At the same time the gross lesions become more pronounced. While the prolonged disease gives rise to more conspicuous lesions, the shorter period yields a larger crop of colonies.

[4] Smith, T., and Fabyan, M., Centr. Bakt., 1st Abt., Orig., 1912, lxi, 549

The lesions produced are of interest. So far as I have been able to study tissues of inoculated guinea pigs no invasion and multiplication within epithelial cells has been observed. This unique locus seems to be limited to the bovine chorionic membrane. The lesions wherever found consist of a diffuse multiplication of local reticulo-endothelial cells or of an infiltration of mobile cells or both combined. A section of a lymph node showing no abnormality excepting a slightly larger size brings out this diffuse general replacement of the normal lymphocytes by the larger monocytic type of cell. This change goes on in lymph nodes, spleen, and the interstitial tissue of the epididymis. In the liver minute depressions indicate the prompt arrest of a process probably due to emboli from the large spleen. The sometimes enor-

TABLE 1

Cows with moderately high agglutinin titer

UDDER QUARTERS	CULTURES OBTAINED THROUGH GUINEA PIGS (+)	
	No. 696	No. 1486
Right fore	−	−*
Left fore	−	−*
Right hind	+	+
Left hind	+	−*

* Another organism simulating *B. abortus* obtained.

mous size of the latter organ is due to interference with the circulation through the formation of epithelioid foci. I have gone into this phase of the subject somewhat in detail because, in view of the probable failure of other methods, we may be compelled to depend upon the induced disease in guinea pigs, and perhaps in other small animals still to be discovered, for guidance in differentiating the races of this species.

We have no reason to assume that *B. abortus* is shed in any large numbers from the infected udder. As an illustration I quote the results of two recent tests for the presence of *B. abortus*. Eight guinea pigs received into the abdomen either cream or mixed cream and sediment or whole milk in 5 cc. amounts. The result is shown in table 1.

It will be noted that milk from the fore quarters failed to infect guinea pigs. Milk from both hind quarters of one cow and only the

right hind of the other produced the typical lesions in guinea pigs from which *B. abortus* was isolated. In the guinea pigs from one of these cows killed five weeks after the injection, a minute bacillus morphologically like *B. abortus* was isolated from the spleen of three animals. Evidently this organism originated in the udder and was able to maintain itself in the guinea pig for a long period. A hasty microscopic examination of the cultures might lead one to assume the presence of *B. abortus*. The organism actively ferments various sugars and is thereby readily differentiated from *B. abortus*. Following inoculation of the bacillus in pure culture into guinea pigs it was not recovered a second time.

The number of cows, aborting or presenting a high agglutinin titer of the blood serum, which shed *B. abortus* in the milk has been found quite variable. Some writers have reported between 80 and 90 per cent, others down to 34 per cent. An important aspect of the public health problem lies embedded here, for it might be claimed that in view of the general immunity of workers with infected material from fetuses and of veterinarians handling adherent diseased fetal membranes so frequently in their practice, the placental strain is harmless to man whereas the prolonged multiplication in the udder might cause a change favorable to invasion of the human subject. In the udder ducts we have also to deal with association of *B. abortus* with a variety of other bacteria, such as streptococci, staphylococci, *B. pyogenes* and others, and some modification due to such contacts might take place. Changes bearing on cultural and pathogenic characters have not been noted however.

In recent years vaccines have been used quite extensively both here and abroad. These consist of living cultures, either virulent or attenuated under cultivation. Such vaccinal strains may enter the udder and continue to multiply in the ducts and acini for we have isolated them from the milk of vaccinated animals. We may also enquire whether the lowered virulence of the cultures may not favor infection of man.

The porcine variety of *B. abortus* has been under observation since 1914 when J. Traum first isolated it from swine. Since then it has been encountered in various states of the Middle West and the Pacific Coast. Reports of tests on guinea pigs from various sources have

been more or less in agreement. It has been more virulent; that is, the lesions have been more conspicuous, subject to softening and abscess formation, and rather widely distributed in the lymph nodes as well as in spleen, testicles, and limbs.[5] The writer received from the late Dr. E. C. Schroeder of the United States Bureau of Animal Industry a number of swine strains which he himself had studied on guinea pigs and found more virulent than the bovine strain. Although these cultures were somewhat old their behavior in guinea pigs could be distinguished by the larger foci with tendency to softening in lymph nodes and a greater involvement of the liver with such foci. In 1927 the writer was able to isolate a strain during the prevalence of porcine abortion in a herd in New Jersey. The still unpublished data may be briefly summarized. The organism was readily recovered from the viscera of the fetuses, even from the heart's blood. It multiplied readily in unsealed tubes of agar. Its effect on guinea pigs was the same as that produced by bovine strains plus larger foci in liver and lymph nodes. The strain was less virulent than those porcine strains already studied but more so than bovine strains.

Of the three animal races of *B. abortus* I assume that the bovine and the caprine races have been adapted to their respective hosts through long series of passages. The porcine race may be a more recent adaptation from the bovine originating in the Middle West where the opportunity for the mingling of cattle and swine on a large scale is given. This supposition is supported by the fact that it has not thus far been encountered in Denmark or in Germany where animal diseases are very closely watched. The strain isolated by me may be a more recent adaptation from the bovine than the earlier western strains. The gradual adaptation and modification in swine may be associated with an increasing invasiveness towards man and virulence for the guinea pig.

The caprine race of *B. abortus* has been much less thoroughly studied in some of its phases than the bovine disease, although longer under observation. We know nothing definite concerning its behavior in the guinea pig, nor of its relation to disease or abortion in the goat beyond casual statements. Its frequent presence in the

[5] For a review of the literature, see J. Exp. Med., 1926, xliii, 215.

goat's udder was determined early together with many other data by an English Commission working in Malta but facts bearing on differential characters were not gathered, because at that time nothing was known of its relation to the bovine disease and for the time being the bacillus, then called micrococcus, stood out unique in the known microbic world. The occurrence of Malta fever in this country traced to goat's milk has been recorded by various writers during the present century. The foci of the human disease are some of the southwestern states, more particularly Arizona, New Mexico, Texas and Mississippi. Goats carrying the infectious agent were imported from Mexico into the United States for many years. In this published material we miss the data necessary for a comparative study of the caprine and the bovine strains.

The writer has examined one caprine strain isolated in 1921 and received from the Pasteur Institute in Tunis. This strain was entirely innocuous to guinea pigs and not even recoverable from the spleen. This absence of virulence may be ascribed to prolonged artificial cultivation. A second culture was isolated in 1924 by Ten-Broeck in China from a man living on goat's milk. A recent preliminary test on guinea pigs shows this four year old strain to possess pathogenic capacities very like those of the bovine race. *Bona fide* caprine races should, however, be isolated directly from goats if they are to be used in any comparative study.

Among the factors to be used for distinguishing between the races of *B. abortus*, are morphological, cultural or physiological, pathogenic, and serological. Concerning morphological distinctions little can be stated. The organism is very small and slight differences in size not readily detected. It is significant, however, that the caprine race was originally regarded as a micrococcus and is still so denominated by recent writers. Whether a difference in form actually exists here among the races should be more carefully investigated.

The most impressive physiological distinction among the animal races is the relation to CO_2. The use of CO_2 in cultures of various bacteria to stimulate growth began in 1918, but Huddleson[6] appears to have been the first to use it with the bovine race in 1921, interpreting

[6] Huddleson, I. F., Cornell Veter., 1921, xi, 210.

the favoring action as an adjustment of the pH of the medium. The refusal of *B. abortus* to multiply in ordinary cotton-plugged culture tubes was noticed by B. Bang in 1897. He used deep serum-agar cultures. Later Nowack found that a culture of *B. subtilis* placed with the medium inoculated with *B. abortus* in a closed receptacle would start and promote multiplication. This was at first regarded as an indication that a reduced oxygen tension was necessary. Hence in 1911, Fabyan and the writer sealed the culture tubes with sealing wax and obtained growth. This method is not quite so universally successful as the use of CO_2. Owing to the wide variation in the amount of this gas which favors growth as well as a fairly wide pH zone of the medium within which *B. abortus* multiplies, the simple explanation of an adjustment of pH by CO_2 is not tenable. Freshly isolated bovine races have been encountered now and then without the CO_2 requirements, but the use of saprophytized strains as vaccines may explain such occurrences. After prolonged artificial cultivation for at least six months, it may be possible to obtain a feeble growth in the usual way. After variable periods of months and years all strains multiply without seal or CO_2. In this stage, sealing actually interferes with the most vigorous growth. Concerning freshly isolated caprine strains no statements are at hand. The inference to be made is that the goat strain is cultured from the start without the devices mentioned. All reports on the isolation of porcine strains from swine agree that CO_2 sealing is unnecessary from the start.

Coming to serological procedures, we may state in general that there is no distinction to be made among these races or among the strains from undulant fever by means of direct and cross agglutination. On the basis of absorption tests Miss Evans has formulated several groups. To be demonstrative the agglutinin absorption procedure must be carried out in many combinations. Miss Orcutt[7] working under my directions was unable, for instance, to note any differences between two human strains and two bovine strains, although, as will be shown farther on, the pathogenic activities of the human strains departed widely from those of the bovine. Further tests are under way in which certain irregularities have been observed

[7] Smith, T., J. Exp. Med., 1926, xliii, 207; and Orcutt, M. L., ibid., 225.

which may explain some of the serological results on record. These pertain chiefly to spontaneous clumping of old strains.

The pathogenic properties of the bovine and porcine strains have been briefly referred to above. It was stated that porcine strains produce more marked lesions in guinea pigs which tend to suppurate. The greater virulence of strains from swine has been observed by earlier workers. Of the caprine races we have no definite information which can be used comparatively in evaluating relative virulence. In general it may be said that cultures shoud be tested as fresh as possible, perhaps within a year of the date of isolation. The comparison of old strains with those freshly isolated may lead to false issues, since a strain highly virulent at the start may appear like a freshly isolated strain of low virulence after prolonged artificial cultivation.

Coming now to the subject of undulant fever in man we have a considerable background of studies on the human disease as produced by the ingestion of goat's milk. Since 1913 various publications have appeared dealing with the goat disease in man in Arizona, New Mexico, Mississippi, and Texas. So far as I know no thorough investigation of this disease and the associated organism in goats has been made very recently. In view of the potentialities of this group of bacteria this is highly desirable. It was not until 1922 that a case of undulant fever in man outside this endemic area was brought to light in the Johns Hopkins Hospital and described by Keefer.[8] This was the starting point for a number of discoveries of similar character. Probably more than a hundred cases arising within the United States are now on record. A large number of human cases have recently been uncovered by the agglutinin test in Denmark. Scattering reports are coming from Germany. It is not my purpose to go into any analysis of this material. Drawn into it by what appeared too hasty conclusions concerning the relation of the bovine race to the prevailing disease, I have been content to point out gaps and discrepancies in the evidence presented and emphasize the need of further study both of the cases clinically and of the associated organisms. Owing to the numbers now engaged in this field we may expect

[8] Keefer, C. S., Bull. Johns Hopkins Hosp., 1924, xxxv, 6.

in due time a more precise allocation of the human cases to the respective animal races of *B. abortus*. The inferences drawn in many of the publications on the sources of undulant fever in man are based on the identity of agglutinins in the strains from animal and human sources. Although this identification of agglutinins with the strains giving rise to them has been a basic assumption in serology, it is subject to limitations like all cultural and pathogenic likenesses and must be applied with discretion. There is no doubt that the agglutinins appearing as a result of infection with bovine, porcine, and human strains fail as a rule to discriminate among the latter. The direct and cross agglutinations agree closely. The absorption process has also been found to show no differences in the few strains to which we have applied it. However, certain groupings have been created by Miss Evans on the basis of absorption differences which allocate certain human cases to the bovine type.

About 23 strains of human origin have passed through my hands. They have come from various observers who, knowing my interest in the animal strains, kindly sent them to me for comparative study. Of these, 18 were isolated from patients in the United States. The remainder came from other countries. Some of the American strains have undoubtedly been studied by others. It would be going beyond the limits of a single lecture to speak in detail of these strains. I shall give only a brief review of our own studies.

There were no CO_2 inhibitions in any of the American cultures when they were received. Some cultures were perhaps too old to manifest this peculiarity. Some were not. In view of the fact that the swine types have not shown this growth requirement from the start this point is significant.

The pathogenic activities as developed in guinea pigs showed much variation. None of the strains were old enough to have lost such activities in any large degree. A rough grouping only can be attempted as follows:

a. No effect whatever on guinea pigs and no recovery of the injected bacilli from the entire spleen. Three strains.

b. The usual more or less variable enlargement (congestion) of the spleen, slight enlargement of lymph nodes, atrophy of testicles. Here we

must remain somewhat in doubt whether attenuation had taken place. One strain.

c. The usual lesions accompanied by small necrotic foci in spleen and lymph nodes. Four strains.

d. The usual lesions accompanied by relatively large or numerous small necrotic-suppurative foci. Ten strains.

The entirely negative outcome of inoculation into guinea pigs with infected tissues or cultures even in high dilutions has not occurred in hundreds of bovine cases in my experience. Even when the lesions, such as spleen swelling, are slight, the organism is recoverable from the spleen two to three months after inoculation. Strains three to four years under cultivation still respond to these tests. The nature, therefore, of the three strains with entirely negative pathogenic characters is left in obscurity. The strain under (*b*) may or may not be a bovine strain. The groups (*c*) and (*d*) I should regard as either not bovine or as bovine modified by passage through swine or perhaps other species. They differ markedly among themselves. Two of these were studied rather carefully in close association with two bovine strains and the results have been published.[7] The lesions were strikingly different from those due to bovine strains. The lymph nodes were relatively very large and completely softened. Necrotic-suppurative foci occurred in the spleen. In fact, the gross appearances of the guinea pig lesions were such as to give me the impression that I had a wholly different disease entity to deal with. Both patients had been in contact with swine material.

One group of five cultures coming from the same locality and from cases occurring at short intervals are of special interest in so far as the guinea pig lesions all presented certain peculiarities. Besides the focal lesions in spleen, lymph nodes, and testicles, the thymus lobes were either permeated with small abscesses or else these had fused and produced a single large abscess about 1 cm. in diameter. Although presumably the result of drinking raw milk these cases are explainable as not truly bovine.

Another strain from a midwestern state presented lesions, which, encountered a generation ago, I should have regarded as due to the glanders bacillus. In fact such diagnoses may have been actually made in the past owing to the negative cultural characters of both

species of bacteria. The guinea pigs became emaciated and one died in two months. The other at this time was much emaciated and was killed. In both the testicles were converted into large abscesses. The fore and hind feet were swollen and covered with small ulcers. Of the many hundreds of guinea pigs which we have inoculated with bovine material or cultures none have died.

Five human strains from European sources came into my hands, one from the Institut Pasteur at Tunis; one from Dr. Duncan of the London School of Tropical Medicine, which had been isolated from a patient infected in Rhodesia; and three from Dr. Kristiansen of

TABLE 2

Strains from undulant fever (Denmark)

CULTURE METHOD	DAYS OF INCUBATION AT 37°C.		
	No. 18	No. 19	No. 20
a. Cotton plug + some parafin	Growth in 3 days	No growth in 12 days*	No growth in 12 days*
b. Sealed with sealing wax	Growth in 4 days	No growth in 12 days*	Growth in 12 days
c. In 10 per cent CO_2	Growth in 3 days	Growth in 3 days	Growth in 3 days

* Developed in CO_2 atmosphere after 12 days.

Denmark. The two first mentioned strains were about two years old. In both the lesions approximated closely to the bovine standard.

The three strains from Denmark are of special interest. Although probably one and a half years old, two of these still showed a marked demand for CO_2 while the third grew equally well in the ordinary cotton-plugged tube, as is indicated in table 2.

After twelve days' incubation, the three still sterile tubes were placed in an atmosphere of 10 per cent CO_2. The originally sealed tube developed a film of growth in three days; the others after six or seven days in CO_2. Probably some bacteria had survived in the condensation water of these latter partly dry tubes. The table furthermore makes it clear that while CO_2 universally favors growth the method does not make as sharp distinctions as the sealing. In fact,

no distinction could have been made between the partially saprophytized (No. 18) and the other strains if CO_2 had been exclusively used. In general a distinction between the lesions produced by two of the Danish cultures subject to CO_2 requirements could not be differentiated from those of the bovine type. The third strain, however, produced no lesions in guinea pigs and could not be recovered from the spleen. It may have been a highly saprophytized, perhaps vaccinal, strain of *B. abortus*.

These illustrations must suffice to point out the want of uniformity in the pathogenic capacities of the strains derived from human patients and emphasize the need for more work in locating the sources. The inferences to be drawn from the labors of bacteriologists up to the present may be briefly presented.

1. Bovine strains or strains not distinguishable from them have been cultured from human patients in a small per cent of the cases studied.

2. The caprine strains isolated directly from goat's milk need more detailed study before we can use this type in comparative studies or allocate them to human cases of undulant fever in man in territories ostensibly free from milk goats or the fresh products of goat's milk.

3. The cultures isolated from man and presumably ingested in cow's milk but not fitting the bovine type, may have been swine strains introduced into that receptive organ, the cow's udder, just as hemolytic and scarlatinal streptococci may gain a foothold in it under certain unknown conditions and cause localized epidemics in man. This view is supported by the rather remarkable drift of the infecting organism of five human strains from one locality into the thymus of inoculated guinea pigs. The characters of strains from such local groups of cases should be more thoroughly studied since it may be possible to locate the infecting cow and isolate the organism directly from the milk.

4. The partly saprophytized cultures which have been used on a large scale in vaccinating cows against infectious abortion may be another possible source of bovine strains. It is conceivable that artificial cultivation in a certain stage may prepare an organism otherwise incapable of multiplication in a new host. It is also possible that some porcine strain may have been distributed as a vaccine in

cows. The third saprophytic, non-virulent Danish strain described may be a vaccinal strain. Some slight change may have in some way favored the infection of human beings in laboratories with glanders during the wide prevalence of this disease in horses towards the close of the nineteenth century, for these cases seemed to be out of proportion to the number of people who became infected while tending glandered horses.

The two sites of *B. abortus* in the cow are the fetal membranes and udder ducts and acini. The question will naturally be asked if the sojourn of *B. abortus* in the udder modifies the uterine type and perhaps makes it more invasive for man. This problem already referred to has been kept in mind during our work with this race. No modification of virulence or CO_2 requirements has been noticed except in a few instances readily referable to a vaccinal strain used at certain periods. Further careful studies are desirable, however, but only in herds not subject to vaccination with living cultures.

5. The swine type of *B. abortus* may have been developed in the mid-western states in recent years, for here the enormous development of the swine industry, the feeding of by-products of the dairy, as well as association between the two species in feed lots, have given Nature numerous opportunities to form new varieties. The relationship is further emphasized by the serological classification of bovine and porcine races together by Miss Evans. The varying virulence of the porcine races may be due to varieties not yet fully adjusted to the new host. Another reason for proposing this genetic source of the porcine type is the reported absence of this type from European countries, where the live-stock conditions mentioned are realized only to a very slight degree. It may be stated in passing that the great increase in swine tuberculosis in the Middle West in the recent past was definitely traced to the intimate association of cattle and swine.

6. The further internal differentiation of the non-bovine types found in man suggests other possible forms of aberrant parasitism of a more or less permanent character developing locally in rats, mice, wild rabbits, ground squirrels, and the like, some of which species may be more receptive to the porcine than to the original bovine races.

7. The gradual development of the milch-goat industry in northern states needs supervision as a possible source of human disease.

In the further unraveling of the sources and significance of this new disease, declared by Etienne Burnet to be the disease of the future, the clinician can be of great service in obtaining as accurately and fully as possible a history of the patient's environment and habits with reference to foods and contact with domestic animals. From the clinical standpoint it is furthermore desirable to obtain cultures of the hypothetical organism, which has been done in only a small per cent of cases, and to standardize serological methods. It is also highly important to determine if possible how far undulant fever is a primary disease and how far merely grafted on other favoring pathological states. A detailed search of hospital records during the past thirty years may perhaps assist in explaining why undulant fever has not been recognized until recently.

I have purposely refrained thus far from bringing in so-called epidemiological data. It should however be mentioned that the bovine disease has been widespread in the United States and that until recently very few if any dairy herds were free from it. I have evidence of its existence from laboratory tests on guinea pigs as far back as 1893. The ingestion of the bovine type by man must have been nearly universal since this early date. How can we explain the scarcity of the human affection even today when attention has been thoroughly focused on it and when it is being diagnosed and perhaps overdiagnosed? How can we explain the freedom from disease of laboratory workers and tenders of dairy cattle, of veterinarians handling diseased tissues and cultures without more than the usual precaution of cleanliness? How can we explain the freedom from disease of groups of adults and children drinking raw milk from herds in which nearly every first pregnancy terminated in abortion?[9] The explanation nearest at hand is that the bovine type is so slightly invasive for man that it fails to produce appreciable disturbances but that as a by-effect it may immunize towards the more virulent types of swine and caprine origin. The evidence brought together points first to the stability of the bovine race of *B. abortus* as isolated directly from bovines, and second to a number of divergent pathogenic char-

[9] In 1916 Cooledge reported an experiment on 7 human beings each of whom voluntarily drank daily 1½ pints of milk from infected cows over a period of 8 weeks. No febrile states were observed. (J. Med. Research, 1916, xxxiv, 459.)

acters isolated from undulant fever patients, only a few of which have distinctive bovine attributes.

Knowing so little of the life of microörganisms outside the narrow confines of the laboratory we are at a loss to explain the situation except by hypotheses which might serve as a formulation of problems to be attacked rather than as a final explanation of the precise sources of undulant fever. The recent history of this disease stresses again the significance of animal life in the development and maintenance of infectious agents capable of starting disease in man. It is of interest to note that nearly all human diseases traceable to animals are septic in type, with a definite invasion of the blood, and some of them highly fatal.[10] May it not be possible that the highly virulent pandemics of the human race, coming as they do from regions where man lives in close association with animals and hunts them for food, are due to organisms reinvigorated by passages through animal species. We know so little of the flora and protozoan fauna of domestic and free-living species that a study in this field may be revolutionary in its results.

In the bovine disease we have touched upon today there is some evidence that, say within a generation, a decline in virulence has taken place. The first case in guinea pigs seen by me in 1893 and some cases in 1911 presented lesions which indicated a much greater invasiveness than any seen in recent years. In these earlier cases the lesions extended to the kidneys and the bones. The kidneys were in an advanced stage of interstitial sclerosis and appeared like two large white tumors. The bones of the limbs and the ribs were the seat of destructive changes. It should be remembered that bovine *B. abortus* may pass from animal to animal as often as the fetal membranes are formed—about once a year. In other words, the passages are more frequent than the life span of the cow. There has been, without doubt, an increasing resistance developed in bovines going parallel with a certain decline in virulence of *B. abortus*. Whether any rise in invasiveness towards man has been associated with this decline may be worth consideration. A general decline in virulence of organisms parasitizing the same host species may be considered as

[10] Smith, T., Bull. N. Y. Acad. Med., 1928, iv, Ser. 2, 476.

deducible from available evidence. To reactivate this virulence some other host may be needed, or more likely Nature from time to time may tap the original source of virulent material in certain animal hosts. In the numerous attempts for increasing virulence or modifying essential functions of pathogenic bacteria by passages through animals in the laboratory a few rather artificial methods are used, whereas in nature a great many different combinations may occur, some one of which may open the path to new physiological races. In this way there may have been formed a number of races of the *Brucella* group for some of which the immediate animal sources are still to be discovered.

As to active measures against undulant fever, if it should be made fairly clear that the bovine race of *B. abortus* is the real source of the other races then the time would be ripe for an active campaign against it. The same should be true for goats if the parent race was harbored by this host species.

THE FUNDAMENTAL FACTORS OF IMMUNITY[1]

FREDERICK P. GAY

It may be rash to attempt to compress into a period of an hour an exposition of what seem to be the essential and fundamental factors concerned in the mechanism by which the animal body protects itself against infectious disease, but I know of no method to clarify one's own ideas and possibly to aid others in visualizing so complicated a subject except by a procedure of this sort, even if the result be open to the criticism of an unjustifiable simplicity.

The science of immunology dates from the early work of Metchnikoff on phagocytosis which began in 1882. We have seen, then, in a period extending for nearly fifty years the building up of a group of thoroughly substantiated, as well as a larger group of less fully substantiated, facts and theories which, in their multiplicity and frequent apparent contradiction, often obscure the real picture that has been defined. There is real danger that we may fail to see the woods for the trees.

METCHNIKOFF'S PHAGOCYTIC THEORY OF IMMUNITY

Metchnikoff was the first to replace the somewhat vague idea of Koch, Pasteur, Chauveau, Naegeli, Grawitz and Buchner as to the mechanism by which animals resist infection by a well formulated theory based on years of increasingly convincing scientific proof which was not only the first complete explanation, but remains practically unaltered and now fully accepted. There can be no question but that the polymorphonuclear leucocytes of the blood stream are able to oppose successfully and to destroy invading bacteria of moderate virulence, and thereby to account in considerable measure for the condition of natural resistance. Metchnikoff, moreover, suggested, but we believe did not sufficiently emphasize, the importance of certain mononuclear cells or macrophages in such chronic bacterial diseases as

[1] DeLamar Lecture delivered before the Johns Hopkins School of Hygiene and Public Health, Nov. 13, 1928.

tuberculosis and leprosy and in the protozoon infections. It is certainly to the polymorphonuclear leucocytes of the circulating blood that Metchnikoff attributes, and we believe justifiably, the first line of defense, if we except those external defenses such as the intact skin and mucosa.

THE HUMORAL ASPECTS OF IMMUNITY

The importance of Metchnikoff's conception seemed temporarily diminished, but eventually became enhanced and complemented by the increasing recognition of the defensive powers of the fluid elements of the blood which we may date arbitrarily as beginning with the work of Von Behring and Kitasato in 1890 and of Buchner in 1891. Not only does the blood plasma and serum of normal animals have the property of destroying numerous bacteria, but these properties are markedly increased by a recovery from many infectious diseases, and they become further exaggerated in those conditions of hyper-immunization produced by repeated injections of bacteria and bacterial products. We have come to recognize and to utilize in diagnosis and therapy these increased, or often apparently newly invoked, physiological properties, inherent in blood fluids to which the name of "antibodies" is usually given. This term is probably a misnomer in that we are dealing with functions rather than structures. Certainly, we are not dealing with structures in the morphological sense as might be gathered from the diagrams of Ehrlich, and we are not dealing with new chemical structures or rearrangements in any sense that we have learned to recognize. At all events, it is through their altered or increased functions that antibodies act antagonistically to bacteria and other foreign cells. If we retain the convenient term, antibody, we find that we have learned to know what seem at first glance a series of different antibodies—antitoxins, lysins, tropins, agglutinins, precipitins, and perhaps anaphylactic antibodies. These antibodies have been commonly separated on the basis of their mode of action which requires, in each separate group, a different set of environmental conditions depending on the physico-chemical state of the antigenic substance that has given rise to them, and the factors concerned and essential for the observed phenomena. Thus it is found that lysins, at least, require an adjuvant factor for ultimate efficiency, and it may be that

tropins are at least facilitated in their activity by the same factor, whereas the other antibodies produce their results without this particular aid, although they require the presence of an electrolyte. It has been the natural tendency of individual discoverers, working as they inevitably do, under a set of conditions which alone produce the phenomenon for which they are responsible, to assign an individuality to the phenomenon they describe. In the course of time, it has become evident that what were originally regarded as separate and distinct antibodies may, in reality, be a single antagonistic function, modified by the conditions in which it operates. Thus, for example, it was at one time assumed that Wright's opsonins, both natural and immune, differed from the tropins of Neufeldt and Rimpau, based largely on an incomplete analysis by Wright of the apparent thermolability of his normal opsonin. Later it was shown by Cowie and Chapin that the apparent disappearance of the normal opsonin by heating to 56°C. was, in reality, simply the destruction of the normal alexin which left a relatively weak but thermostable antibody. This weak antibody in normal serum is increased by immunization until it becomes sufficient in itself to produce a change in bacteria so that they are more readily phagocyted without the presence of alexin, but there is evidence to believe that the alexin increases the attractiveness of treated bacteria even in the case of immune serum and the combined action of alexin plus thermostable body is necessary to produce the opsonic effect. By simplifications of this sort, the analysis of antibodies has proceeded to the point where many of us are prepared to regard them as essentially identical. Zinsser has given us very persuasive evidence of this undoubted trend, and I should be willing to go even further than he does and include in the unification, antitoxins as well as the substances acting more directly on bacterial bodies. There has been from the very beginning little dispute as to the essential identity of agglutinins and precipitins. Agglutinins affect bacteria and other cells in such a way that in the presence of an electrolyte they flocculate. Precipitins in similar fashion flocculate bacterial extracts and other protein molecules in solution. Both phenomena when studied in different concentrations of the reacting substance present alternate zones of inhibition, due to stabilizing colloids, and of flocculation. In a similar way it is not difficult to consider

tropins and lysins as essentially identical. Both unite with bacteria, with red blood cells or other formed elements, so that the latter either become more attractive for leucocytes (tropins), or are rendered more readily destroyed by the alexin which is a normal constituent of plasma and serum. I have given an indication that the tropins, although they function even after moderate heating, act better when alexin is present. There is evidence in both the phenomena of lysis and tropinization to show that a diminution of the second factor, alexin, may be compensated for within certain limits by increasing the thermostable factor, sensitizer, or tropin, and it is likewise true that a diminution of the sensitizer may be compensated for by increasing the alexin.

It is perhaps more difficult to accept antitoxins as identical with the other antibodies we have just mentioned. Its function is to neutralize, or better to form a neutral complex with an antigenic derivative of bacterial metabolism, so that this toxin must be a substance essentially analogous to the precipitinogen. The recently established parallelism between flocculation of toxins and antitoxins (Ramon) and the neutralization of the toxin itself may be evidence of the identity of the two substances. In a similar way, the anaphylactic antibodies are either parallel to or identical with precipitins. Of course, the main contention of the separateness of the various antibodies has lain in a lack of parallelism between the demonstrable occurrences of reactions characteristic of these antibodies in a course of immunization. That is, agglutination may appear before sensitizing or tropinizing effects are evident, but here certainly the great dilutions that suffice in demonstrating agglutinins and the relatively greater concentration required to demonstrate lytic phenomena might explain their apparent successive appearance. As Zinsser has pointed out, the unitarian theory of antibodies does not exclude the production of a series of antagonistic substances, each active against a constituent protein in complex cells such as typhoid bacilli, nor the production of separate precipitin antibodies against each of the separate protein fractions in a complex mixture like blood serum. But what is meant is that a single antigen in a pure state produces only one variety of antibody, and that antibody may be demonstrable in the form of the several different reactions, such as agglutination, precipitation, and sensitization, depending in turn on the structure of the antigen and the environmental conditions under which

the observations are made. In order to produce the complete phenomena, alexin may be required as in lysis, and possibly in the action of tropins or simply an electrolyte as in the case of agglutination, although even here the fact that heating does diminish the agglutinin titer may show that alexin facilitates the reaction, and again although alexin may not be needed in the precipitin reaction, precipitates certainly fix it.

It seems more profitable in attempting to visualize the humoral aspect of immunity to emphasize the similarities in the so-called antibodies rather than their differences. These points of similarity are briefly as follows: Antibodies are produced only by proteins in a certain colloidal condition, or perhaps by proteins to which lipoids or carbohydrates are attached. Secondly, antibodies are characterized by a specific union with the antigenic substances, which union takes place in variable proportions in accordance with the mode of combination employed. Thirdly, the complex of antigen and antibody tends to dissociate, as may be evidenced not only by the effect of heat, acid, or dilution on mixtures of toxins and antitoxins, but by the active immunizing power—that is to say, dissociation in the animal body, of neutral mixtures of toxins and antitoxins, and also of sensitized vaccines. And finally the antigen antibody complex is endowed with new properties of attraction for alexin or for leucocytes.

In addition to the so-called antibodies, the humoral protective forces of the body include certain other factors. Most prominent among these is alexin or complement which is not increased as a result of immunization. In addition, there is the so-called "cytase" of Metchnikoff which may be extracted from mononuclear and polymorphonuclear leucocytes, and which apparently differs from alexin in that it is thermostabile. This substance would seem to account for the destruction of bacteria in phagocytes but it may be questioned how representative an extract of artificially disintegrated leucocytes is of what takes place in the living cells. There are probably other substances that contribute to protection such as the anthracidal substances in the serum of certain animals, and the conglutinin of bovine serum, both of which are likewise thermostabile.

The antibody properties in acquired immunity are indicative of a reaction that has taken place to a foreign protein. They are certainly

not exact measures of the protection itself, and we should be inclined to think that under natural conditions of recovery from disease they are operative only as accessory factors, rather than as primary factors of the increased protection afforded. Protection may exist without marked antibody content, and considerable antibody content may be present without protection. We are inclined to refer the essential protection to some change in the body cells. It should not be overlooked that antibodies have been studied particularly as they occur under conditions of hyperimmunization which do not represent immunity, however durable, as acquired by recovery, but an artificial intensification of it produced by inoculation of enormous amounts of antigenic substances. That does not mean that the property so produced by hyperimmunization may not be very valuable in producing passive immunity by injecting the serum of hyperimmunized animals. It would seem most likely that the failure of the majority of anti-bacterial serums to act therapeutically is due not to their lack of antibody content but to failure in qualitative or quantitative preparation on the part of the cells of the recipient. We think of antibodies then simply as reflecting a more fundamental and essential process that has gone on somewhere in the body cells, this cellular reaction being, we believe, the essential basis of immunity as we shall now proceed to elaborate.

THE OUTSTANDING PROBLEMS OF IMMUNITY

It has long been evident that there are conditions of protection through recovery that cannot be explained on the basis of Metchnikoff's phagocytes, or the persistence of antibodies. Take for example, the recovery from typhoid fever followed by a most durable and emphatic protection, but not evidenced except in carriers, by a continued presence of antibodies in the serum. The polymorphonuclear leucocytes are certainly not increased in number nor, so far as we know, in quality, and yet the individual is protected. Another instance is smallpox immunity, produced either through vaccination, which means the recovery from a modified form of the disease, or by recovery from smallpox itself. Although viruscidal antibodies can be produced by hyperimmunization and may occur during the course of the disease, there is no evidence that they are present throughout the

course of the durable immunity. It has been customary to explain these very striking instances of protection as due to tissue immunity. It is, we believe, in defining more precisely what we mean by this term "tissue immunity" that the next wave of progress in immunology will come.

It would seem to us that the three major questions in the study of immunity today, an elucidation of which would mean the most significant progress are: first, the nature of specificity; secondly, the locus of origin of antibodies in the immunized animal; and thirdly, the mechanism of local or tissue immunity.

The first of these questions need not concern us particularly at this time. It is generally accepted that proteins almost, if not quite exclusively, are alone capable of acting as antigens. Attempts have been made to detect the antigenic moiety in the complex protein molecule which is responsible for the specific response, either by disintegrating proteins to the stage last producing antibodies, or by combining radicles of the protein molecule in such combination as to originate specific antibody response. More recent emphasis has particularly been paid to modification in the protein molecule by heat, chemicals, and the like, which modify its antigenic property, and particularly the addition of carbohydrates or lipoids to proteins has been studied in this regard. Of particular interest are the so-called haptenes of Landsteiner which apparently have the property of uniting with antibodies but not of producing them. The contradictory bearing of this conception of Ehrlich's theory need scarcely be emphasized.

The problem of the origin of antibodies in the animal body is one of the oldest problems of immunity. Following the discovery of antitoxins, attempts were made to ascertain how these important properties of serum originate, although it was thought at first that a simple transformation of toxin into antitoxin in the blood stream might take place. It was found that the marked disproportion between the antigen injected and the antibodies produced could scarcely be explained on the basis of simple transformation. It was then found that exsanguination with the mechanical removal of a large proportion of antitoxin gives only a slight and temporary decrease of antitoxin in the circulating blood of the immunized animal. This and the stimulating effect of pilocarpin on antibody production indicated inevi-

tably that the origin of these important substances lay outside the blood stream, and by inclusion must be regarded as being due to cell activity. Ehrlich's theory of immunity offered apparently complete explanation of this intraceullular process. In fact its very completeness, in view of the relative paucity of observations at the period at which it was suggested, should have rendered us suspicious of its accuracy, but instead of a suspicion, a remarkably widespread acceptance of Ehrlich's view prevailed, and in our opinion inhibited actual progress by satisfying intellectual curiosity. Investigations for many years were dominated by attempts either to prove or disprove Ehrlich's theory, instead of a continued search for the actual facts. Apparently when antigens are introduced parenterally, that is to say, in complete and undigested form into an animal of another species, they become fixed somewhere in the cells and, it may yet be as Ehrlich assumed and as there is some experimental evidence to indicate, they become fixed in the case of poisonous antigenic substances in those cells which such poisons attack. It is difficult to see, however, how the second phase of Ehrlich's hypothesis, namely the production of antibodies by the susceptible cells, could take place, until convincing experimentation should prove such localized formation. Such evidence, in spite of repeated search for it, has never been produced. The search for evidence of a more direct sort on this problem has not been lacking, but has so far also been without conclusive results. The general methods pursued in such investigations have been the following: first, the search for the point of fixation of the antigen after its introduction into the animal body. Even if this were convincingly shown it would not suffice to prove that, although the antigen were fixed in a particular organ, the antibody is produced there.

Next, the precocious appearance of the antibody has been sought in various tissues particularly in the hematopoetic system, before the appearance of such antagonistic substances in the general circulation.

Thirdly, and correlatively, an attempt has been made to destroy certain parts of the hematopoetic system, as by the action of benzene on the bone marrow, or by simple ablation by the spleen, in an attempt to show that such effect destroys or minimizes antibody production. Our final conclusions from such experiments along these several lines would be that, although suggestive results have been obtained in

the hands of some investigators, no final conclusions can be made as to the production of any particular antibody in any definite organ or tissue. It is our feeling that antibody production may well be a more universally distributed function in the animal body than would be revealed by any of these methods that have been described, and we believe that a suggestive line of inquiry has been opened on this question by means of blockade of the reticulo-endothelial system. This mode of attack, is by no means as yet conclusive for several reasons: in the first place, when we speak of reticulo-endothelial blockade we imply that the substances employed in attempting to produce such a result actually do "blockade" the various types of cells which in their aggregate constitute this supposed system. In other words, reticulo-endothelial blockade should fill up the vacuoles and thereby put out of function the cells of the capillary endothelium, the monocytes, and the tissue macrophages. As a matter of fact, it would seem that the different materials utilized are more or less selectively chosen, each by one of these particular types of cells which have been mentioned. The clasmatocytes of connective tissues ingest and store trypan blue whereas carbon particles seem to locate in the endothelial cells, so that the employment of any one of these substances alone would certainly not suffice to blockade the entire reticulo-endothelial system. And again the complete blockade by methods, usually employed, of even one type of these cells may well be questioned. Our own results indicate that hemolysin production is inhibited by injection of trypan blue in rabbits and rats. Others have obtained no inhibition or indeed an actual stimulation. It is of course not inconsistent that an incomplete filling of these cells should stimulate antibody production whereas complete blockade should prevent it. Certainly here as in other types of experimentation positive results under certain given and controlled conditions, which may not be precisely duplicated in a number of negative repetitions, by no means invalidates the first finding. Certainly continued investigations with various dye stuffs, colloids, and particulate materials are indicated, particularly if such materials can be found as are selectively stored in cells other than the histiocytes.

LOCAL OR TISSUE IMMUNITY

The possible existence of a condition of localized immunity was indicated long before a descriptive term for this condition was originated by Wassermann. This author assumed that a certain "retuning" (Umstimmung) of the cells would account for their increased opposition to a given infectious agent. It was originally shown by Metchnikoff that cells other than the polymorphonuclear leucocytes have undoubted phagocytic properties. His macrophages comprise at least the mononuclear cells of the blood, endothelial cells, and Küpffer cells. As we have already indicated, Metchnikoff assigns to these cells phagocytic properties, particularly for the cells of foreign animal species, for the microörganisms of certain chronic infections, and for protozoon parasites. The protective significance of the mononuclear cells which follow the polymorphonuclear cells into the serous cavities in acute bacterial infections was also recognized by Bordet in studies with the streptococcus, and by many others. In other words, whatever may be the importance of the polymorphonuclear leucocytes, the mononuclear cells have been understood as forming the second line of defense either by direct ingestion of infectious agents, or by the secondary ingestion of such agents already phagocyted by the polymorphonuclear cells.

Our own studies with the streptococcus in rabbits have led us to regard these mononuclear cells as the sole important element in combatting the particularly virulent type of organism with which we were working. We found not only that a local immunity of the skin in experimental erysipelas could be produced, but that a relatively localized protection of the pleural cavity could be created, not only by injection of the specific streptococcus, but by such indifferent materials as aleuronat and broth, provided the proper interval is chosen. Protection in all these instances was paralleled by the predominance, or at all events by an adequate minimal number, of mononuclear cells in the pleural exudate. Polymorphonuclear cells in this instance have no protective value. It was easy to prove that the mononuclear cells are essentially the histiocytes of connective tissue which must be derived, not from the circulation, but from adjacent structures. The next subject in our analysis was the proof that the actual protection in the pleural cavity under these conditions, although reflected in the

exudate, was due to the formation of granulation tissue in the parietal pleural wall. Granulation tissue in general has long been recognized as resisting bacterial infection, but it remained for recent studies, including our own, to recognize that the resistance of such granulation tissue to certain bacteria is due to histiocytes and not to other cells in such a tissue.

It was subsequently possible to prove that the granulation tissue in the pleural cavity does not act simply as a mechanical barrier, but rather in virtue of the phagocytic activity of its constituent clasmatocytes. This could be shown by the fact that such cells mobilized in one pleural cavity may be moved to the other pleural cavity, and there likewise produce protection. Subsequent experiments have shown that similarly mobilized cells in the omentum and peritoneal wall may progress through the diaphragm to the pleural cavities and protect, and they may actually be transferred from one animal to another by means of omental transplants (Linton). It is possible indeed to transfer such protection from one animal species to another species (guinea pig to rabbit).

This type of protection against an acute bacterial infection is due to the one group of cells that can with certainty be identified by vital and supravital stains. Apparently this protection is due to a quantitative increase of these cells and their mobilization, rather than to a qualitative change in them. It by no means proves that other bacteria are affected in the same way as is our streptococcus. In fact, in the hands of Chesney, granulation tissue, produced to be sure in a different way from our own, is readily penetrated by the *Treponema pallidum* and by the *Pasteurella aviseptica*. We have confirmed certain of these results. This only indicates that we should study other groups of cells, for increased protective functions of this sort with various bacteria. The cells that we have employed, the clasmatocytes, have the advantage of greater resistance (Lewis) and of a distinct property of mobilization, but it may well be that more fixed tissue cells have similar properties. We like to think of this line of experimentation merely as introductory to what may be referred to as the histology of immunity, and as perhaps leading to a more complete understanding of the fundamental properties of the tissues underlying antibody formation and active phagocytic defense.

HERPETIC INFECTION, WITH ESPECIAL REFERENCE TO INVOLVEMENT OF THE NERVOUS SYSTEM[1]

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The disease which constitutes the subject of my discussion, namely herpes, is a member of a large group of maladies of unknown etiology which includes within its wide boundaries many important examples, occurring not only in man, but in the lower vertebrates, insects, plants, perhaps even among bacteria as well (33). The proper members of this group have as their cause specific active agents which have been shown to be passable through earthenware or porcelain filters with sufficiently small pores to hold back most of the ordinary types of bacteria. The members of the group are therefore designated at present filterable virus diseases.

It is an honor to this institution that its leadership has recognized the very great importance of filterable virus diseases, as promising subjects for especial study, by creating the first Department of Filterable Viruses, which has served to focus upon this field the attention of many investigators in this country.

The known parasites of infectious diseases fall into two great groups, namely *plant* parasites, such as the bacteria and fungi, and *animal* parasites, particularly the protozoa.

The biological nature of the specific parasite of a disease has been determined in the main by cultivating the causative microörganism on suitable artificial media outside the body of the host, as with the bacillus of typhoid fever, or by a study of the form of the infecting agent in the blood or tissues of the host, as in the case of the plasmodium of malarial fever.

Notwithstanding the large number of diseases which in recent years has been scientifically classified in this way, on an etiological or

[1] De Lamar Lecture delivered before the Johns Hopkins University School of Hygiene and Public Health, February 26, 1929.

causal basis, there remains the important group of filterable virus diseases which appear to be infectious, and are often the most contagious of diseases, whose causative agents have neither been cultivated on lifeless media nor yet identified with certainty by means of the microscope. The filterable viruses are known only through the changes which they induce in certain cells of the host (14). There is often a striking specificity of effect of a virus on certain types of cell. This is seen in such filterable virus diseases as rabies and acute anterior poliomyelitis, in which the specific viruses affect particularly, and possibly only, the cells of the nervous system. Characteristic for such filterable pathogenic agencies is that they increase in quantity in close association with the cells which they specifically change. The viruses frequently bring about structural alteration of the cells which are often specific for the virus concerned (32).

Due to the fact that the viruses have never been cultivated on lifeless media, and that nothing of sufficiently distinctive form has ever been seen in the diseased tissues to prove their parasitic nature, two divergent views have arisen concerning them. One view is that they are extremely small living parasites, escaping detection or recognition because of their size, which grow within, upon, or in very intimate relation with, the cells of the host (14). Another view interprets them to be non-living agents of the nature of enzymes, ferments or toxic substances which, when they affect certain cells, cause these cells to reproduce the same non-living active material, thus accounting for the continuous regeneration of the pathogenic agent (34) (6) (29).

In order to prove an etiological relationship of a certain parasite or agent to any disease, it is first necessary to show that the parasite or agent under consideration is transmissible from one individual to another, and that it induces on transmission a corresponding disease in the new host. The members of the group of filterable viruses have thus been shown to be transmissible active agencies. If the virus of rabies, for example, is inoculated into a susceptible animal the disease hydrophobia results and it is associated with characteristic changes in cells of the nervous system. Likewise if the virus of poliomyelitis is inoculated into monkeys (macacus rhesus) nerve changes and paralyses result quite comparable to those of infantile paralysis.

The viruses of these two diseases, rabies and poliomyelitis, belong to the neurotropic group (Levaditi) of filterable agencies, that is, they have an especial affinity for nervous tissue (22).

Recent experimental investigations have shown that the herpetic virus, which causes the common fever blister or cold sore of the lip, is also neurotropic, and it is now classified with the viruses of rabies and acute anterior poliomyelitis. In certain animals, particularly the rabbit, the herpetic virus is often a more virulent pathogenic agent than is either rabies or poliomyelitis in man. Many strains of herpetic virus, if inoculated upon the skin or the mucous membranes of a rabbit, are capable of inducing a rapidly fatal disease of the brain and spinal cord.

The newer knowledge of herpes has come during the last few years. It began with, and was made possible through, the demonstration by Grüter in 1912 that a particle of material from an herpetic blister if inoculated upon rabbits, will cause herpes; and the disease may be transmitted in series, from one rabit to another (19).

The demonstration of the transmissibility of herpes has resulted in knowledge which helps in the understanding of the common herpetic infections of man, and also aids in theoretic interpretations of the activity of other virus diseases.

It is my purpose in this discussion to present some of the recent experimental work on herpes in man and animals, and to consider the possible relationship of herpes simplex to herpes zoster, or shingles, and to epidemic (lethargic) encephalitis. I shall also discuss the pathogenesis of herpetic infection in man.

At the outset it is necessary to distinguish the disease herpes simplex, from the disease herpes zoster, zona or more popularly, shingles. Zoster has not as yet been proven to be transmissible to lower animals, whereas the virus of herpes simplex is readily inoculable upon rabbits and certain other animals (6).

Herpes simplex in man is a disease with a variety of manifestations (35) (24). Everyone is familiar with the general characteristics of the common fever blister or cold sore which occurs so frequently about the margins of the lips. It will be recalled that the eruption is usually localized at one or more points about the muco-cutaneous border. It begins with a somewhat painful swelling which soon

develops into groups of small, watery blisters situated upon an erythematous base. These dry up in a few days and heal without leaving a scar. Some individuals have recurrent attacks; and the eruption may appear at approximately the same site at fairly definite intervals. The herpetic eruption confined to the lips is spoken of as herpes labialis, and on the other parts of the face, as herpes facialis. If it is on the cornea it is referred to as herpes corneae. A similar eruption occurs less frequently about the genitalia and is termed herpes progenitalis. Experiments have shown that virus from each of these forms is infectious to man and rabbits, and there is good evidence that they are all caused by the same active agent (26). These and all other types which are infectious to the rabbit may be referred to under the general name of herpes simplex. In addition to these localized skin manifestations many clinicians have insisted upon the reality of a general reaction caused by herpetic virus which has been named herpetic fever. This has been described by Plessing (24) as follows:

> Suddenly without prodromal symptoms, a patient, more often young and without antecedent sickness, is seized with chills; in a few hours the temperature rises to 40°C. and over. The patient feels fatigued, complains of headache, sometimes with associated joint pains; the tongue is coated and there is a total loss of appetite. One may suspect a grave illness, but in a short time, sometimes at the end of the first day, often upon the third day, the fever falls and the patient recovers. However, there appears, generally after the third day and in uncomplicated cases, after the rise in temperature, a facial herpes (labial or nasal). The disease ends with the desquamation of the lesions.

In such cases the throat may be sore and the tonsils covered with minute ulcerations (1). The disease may appear in epidemic form. This clinical condition needs further investigation to ascertain its exact relation to herpes.

Some herpetic eruptions seem to be idiopathic, that is, they do not appear to depend upon nor to be associated with any other pathologic condition. Similar herpetic eruptions are secondary to some other condition. The latter cases may be subdivided into those in which a concurrent infectious disease is evident, and those which are dependent upon an intoxication induced by chemical means. Among

the infectious diseases frequently accompanied by herpes are pneumonia, cerebrospinal meningitis, malaria, influenza and infectious jaundice. The chemical intoxications which predispose to an herpetic eruption are those caused by proteins, for example vaccines and foreign serums, and by certain drugs such as arsenic, cacodylate of soda, salvarsan, iodine, lead and morphine. Almost any morbid state may at times be accompanied by herpes. The diversity of conditions which appear to initiate an herpetic eruption would seem to necessitate the assumption of a very wide dissemination of herpetic virus or a very ready generation of it spontaneously. Recurrent herpes breaking out at almost exactly the same cutaneous site at monthly or even yearly intervals suggests very strongly that the virus may be harbored locally in a latent form for long periods. I shall have occasion later on to revert to these problems.

Much of our recent knowledge of herpes has come through the study of experimental herpetic disease in lower animals, and in order to discuss more clearly the human disease it will be necessary briefly to review this phase of the problem.

Following Grüter's basic discovery of the transmissibility of herpes, the problem was rapidly attacked by experimenters in many parts of the world. Various clinical forms of herpes were proven to be similarly inoculable (26), and the experimental herpetic vesicles were shown to be like those of the human, even in specific cytologic detail (25). In experimental investigations the disease has usually been transmitted by infecting the scarified cornea of a rabbit with material derived directly from the human lesions. Within twenty-four hours after inoculation small watery blisters appear along the lines and points where the corneal epithelium has been injured by scarification. Cellular injury seems to be an important prerequisite to a successful inoculation. Rapidly the clear corneal vesicles rupture leaving tiny ulcers; these extend and coalesce until the entire cornea may become ulcerated. As the intensity of the injury increases a profuse inflammatory reaction occurs in the cornea and the entire conjunctiva, filling the eye with thick pus. Reaching its height in four or five days the inflammation gradually subsides and the eye heals, usually with total loss of vision.

With some strains of virus no other symptoms occur in the infected

rabbits. Doerr and Vöchting observed in their experiments, however, that a few days after infection of the cornea the rabbit would show curious nervous disturbances accompanied by a marked elevation of body temperature. Following a unilateral corneal infection the head would be drawn at short intervals toward the affected side. This symptom during succeeding days would become more intense until loss of equilibrium ensued, and as the head became drawn to the side the animal would fall in the same direction, right himself with difficulty and remain in an upright position only by bracing himself against the side of the cage. Frequent fatal terminations occurred nine to twelve or more days after inoculation, preceded by convulsions with gnashing of the teeth, opisthotonos, and salivation. Doerr and Vöchting proved that the herpetic virus had reached the brain in these instances, and that an acute herpetic encephalitis was responsible for the train of symptoms. The brain contained active virus demonstrable by inoculation upon the cornea or subdurally. Virus from a common fever blister was thus shown to be capable of causing in the rabbit an inflammation of the cornea and conjunctiva terminating fatally in an acute infection of the brain. In some way herpetic virus, initially applied to the cornea, had reached the central nervous system. It proliferated there and injured the nerve cells as it did the cells of the cornea. No other changes were found in the bodies of rabbits dead of herpetic encephalitis which indicated any other local injuries. It seemed therefore that nervous tissue in the rabbit is particularly susceptible to the virus.

The question immediately arising as a result of these observations was, how does herpetic virus from an infected eye reach the brain to bring about an encephalitis. Doerr and Schnabel found that they could induce an encephalitis by introducing the virus into the blood stream of a rabbit. They therefore assumed that herpetic virus invades the blood stream from a diseased eye, causing a septicaemia. It then localizes in some way in the brain from the circulating blood. It is difficult to demonstrate herpetic virus in the blood of a rabbit with herpetic keratitis, and Levaditi was unsuccessful in inducing encephalitis by intravenous injection of virus. As a result of his own experiments Levaditi therefore concluded that virus enters the brain from an infected cornea by a direct invasion along the corresponding optic nerve. Neither of these views however proved to be correct.

Friedenwald found active virus in the Gasserian ganglion following herpetic keratitis in the rabbit and he suspected because of this observation that the virus enters the central nervous system through the sensory division of the fifth cranial nerve which innervates the cornea.

The experiments of Goodpasture and Teague demonstrated conclusively that from an infected cornea the virus does enter the brain invariably by way of the sensory division of the fifth cranial nerve on the infected side, and that it causes a unilateral inflammation about and within the central termination of this nerve in the pons. From this point of entry it spreads within the central nervous system and in fatal cases terminates in an acute encephalitis, particularly marked in the basal region of the cerebral cortex.

It was found that the virus is capable of causing a specific herpetic lesion not only in the cornea, but in many other tissues of the rabbit (15). Following local injection or application of small quantities of virus obtained from an early keratitis, specific herpetic lesions were induced in the rabbit's conjunctiva, retina, buccal mucosa, skin, trachea, liver, adrenal, ovary, brain and spinal cord. These experiments demonstrated that the herpetic virus is not restricted to the skin and the nervous system in its capacity to proliferate and cause lesions in the experimental animal. It was observed further that the virus frequently attacks the spinal cord or the brain following a peripheral inoculation in the tissues mentioned above; and if this event occurs the initial injury in the nervous system takes place at the point where the nerves which supply the peripherally inoculated area enter the spinal cord or the brain. For example if the retina is infected a local herpetic rètinitis results and this is succeeded by a progressive infection of the brain which follows the course and distribution of the optic nerve. An infection of the tracheal mucosa is followed by an encephalitis affecting the medulla oblongata where the vagus nerve is distributed. Inoculated into the masseter muscle on one side the virus traverses the motor division of the fifth cranial nerve and first induces changes in the corresponding motor nucleus on the same side. Infection of the ovary, adrenal or liver is followed by a transverse myelitis affecting that portion of the spinal cord where sympathetic fibers from the infected organs offer channels for conduct-

ing the virus. An interpretation of these experiments led to the conclusion that peripheral nerves, whether sensory, motor or sympathetic, may serve as portals of entry into the central nervous system for the virus of herpes if a local herpetic lesion be induced somewhere in the peripheral tissues (16). The correctness of this conclusion was borne out by the fact that a myelitis of the lumbar portion of the spinal cord could be caused by an inoculation into a muscle supplied by the sciatic nerve, but if the sciatic nerve were severed before the inoculation no myelitis ensued. All that seems necessary to induce an herpetic inflammation of the central nervous system is to bring a suitable strain of the virus into intimate contact with the peripheral nerves or their terminations by means of an injury.

Of course these experiments were highly artificial in that they brought virus into localities and into contact with nerves in a way which would hardly occur under any natural conditions of contagion. Subsequent experiments however threw some light on the possibilities of infecting the central nervous system through contact between infected and non-infected rabbits. Goodpasture found that normal rabbits placed in the same cages with rabbits having a corneal herpes, in the majority of instances, contract herpetic encephalitis in a few days (17). By carefully examining the various nerves which connect the periphery with the spinal cord and brain, it was found that in these contact infections the virus enters the brain through the sensory division of the fifth and the ninth cranial nerves. This was determined by finding the earliest herpetic lesions at the central terminations of these nerves, and in the case of the fifth nerve that portion was affected which supplies the mucosa of the mouth and the nose. It was concluded therefore that in contact herpetic infection in rabbits the virus enters the brain through those nerves which supply the mucous membrane of the mouth and throat. It seemed possible that a similar route might be the portal of entry for the virus of poliomyelitis in certain cases in the human. Marinesco and Draganesco somewhat later also demonstrated that the virus enters the brain following corneal inoculation by way of the sensory division of the fifth nerve. According to their view the passages of transit were the perineural lymphatic spaces.

The experiments of Goodpasture and Teague had indicated that

the virus of herpes increases *within* the cells which it injures and not within the body fluids. Therefore, they interpreted the passage of virus from the periphery to the central nervous system to be not through lymphatics but by way of the axis-cylinder neural processes, which form a direct connection between the injured peripheral cells and the bodies of the nerve cells themselves. This hypothesis was submitted to experimental test by inoculating the masseter muscle on one side and studying the changes in the corresponding motor nerve and the fifth motor nucleus, as soon as an encephalitis manifested itself (18). In suitable experiments herpetic changes were observed within the motor ganglion cells deep in the pons before lesions could be found within the nerve or elsewhere. It was concluded that following an intramuscular inoculation the virus passes directly along the axis-cylinders of the corresponding nerve to the motor ganglion cells, not by a passive transportation but by active proliferation in the intracellular medium represented by the axis-cylinder process. The myelin sheaths surrounding the axis-cylinders seem to insulate the virus in its passage into the brain from the periphery, for it was found that the cells of the sheath of Schwann surrounding the axis-cylinders are susceptible to herpetic virus, and when they become affected an acute neuritis manifests itself. It was possible in these experiments for the virus to affect the ganglion cells in the fifth motor nucleus, after passing through the very susceptible neuroglia within the brain, without causing any evidence of an inflammation of the nerve itself until the deeply embedded nucleus was reached. The progress of the virus within the brain and the spinal cord, once it gains entrance, also suggests that its spread is directed by neural processes and paths.

Herpetic infections in the rabbit do not always lead to obvious involvement of the central nervous system. Some strains of virus are much more neurotropic than others. A well established herpetic encephalitis is not always fatal. Those animals which recover from a peripheral or central infection are immune to reinoculation, and the completeness of the immunity depends considerably upon the extent and duration of the original infection. This is in contrast to the apparent absence of immunity following herpes in the human. Teisser, Gastonel and Reilly have shown, however, that on repeated

(4 to 7) infection of persons with autogenous virus a refractory state may be induced. The immunity, however, is of short duration (in one patient 15 days). While refractory to inoculations with their own strain of virus, these patients usually remain receptive to the virus from another patient, and their own virus is still infectious for others. Examination of the blood during the refractory state discloses no demonstrable immunity reactions.

Experimental herpetic infections in animals, which have demonstrated so strikingly the tendency of this virus to invade nervous tissues, have focused attention on the possibility of similar extensions of primary infections in the human from a peripheral eruption by way of nerves to neural ganglia or to the central nervous system itself. The evidence is that it may so spread in the tissues of man. While most herpetic eruptions in the human do not have an obvious neural distribution it is not at all uncommon to observe, not only in facial herpes but in eruptions on other cutaneous surfaces, a very definite or a probable relation of the eruption to a particular cutaneous nerve. Teague and Goodpasture described a typical herpetic eruption along the course of the right supra-orbital nerve. Transmissible virus was demonstrated in the vesicles of this lesion by inoculation upon the rabbit. Before the infectious nature of herpes had been established by animal inoculation, Howard had shown that in cases of labial herpes the Gasserian ganglia may show an inflammatory reaction. Injury to a Gasserian ganglion, as observed by Cushing, is not infrequently followed by an herpetic eruption within the field of distribution of undestroyed cutaneous branches, apparently from a central source. Associated with genital herpes an increase of mononuclear cells in the cerebrospinal fluid has been noted (24), and in certain rare instances with or without cutaneous herpes, an herpetic virus has been recovered from the spinal fluid (11).

Since the herpetic virus is capable of penetrating so far as the spinal fluid in the human, and in view of the fact that it has an especial propensity for penetrating the brain and spinal cord in rabbits, inducing frequently a fatal encephalitis, the question has arisen whether the virus may also on occasion attack the central nervous system of man and bring about serious results. This contingency has received a great deal of consideration in recent years since the an-

nouncement by Levaditi and Harvier of the discovery of a virus in the brain of a fatal case of lethargic encephalitis, or the sleeping sickness of von Economo, which was not, in the experience of Doerr, distinguishable from that of herpes simplex. The possible etiological relationship of herpetic virus to epidemic lethargic encephalitis has recently been critically discussed by Flexner, Doerr and by Zinsser. I shall therefore not attempt at present a thorough consideration of the matter.

The basis of fact on which may rest an hypothetical etiological relationship of herpes virus to epidemic encephalitis is the demonstration by several investigators of a virus indistinguishable from that of herpes in the brain or spinal fluid from certain cases of encephalitis. Strains of virus have been isolated by Levaditi and Harvier in France, Doerr and his coworkers in Switzerland and Germany, by Luger and Lauda in Austria and by Perdrau in England (40). On the other hand the vast majority of attempts to recover a virus from what appears to have been equally favorable material have failed (12). This is illustrated by the experience of Flexner and Amoss who have never succeeded in isolating a virus from encephalitis either from the brain or spinal fluid notwithstanding they have made a great many attempts. Those who have been successful, have also met with many failures, and as Flexner has pointed out there have been no doubt numbers of unrecorded negative results. Consequently we must consider the isolation of an herpetic virus from lethargic encephalitis a rather rare accomplishment. Herpetic virus is so infectious for rabbits that were it the cause of epidemic encephalitis one would expect it to be easily demonstrable in the cerebral tissues of early cases of this disease. This, however, is not the fact. It seems quite possible that the successful results were due to the recovery of a latent herpetic virus which had no direct etiological relationship to the encephalitic disease. This is rendered more likely by the demonstration by Flexner and Amoss of an herpetic virus in the spinal fluid of a patient with syphilis of the central nervous system in whom there had been at no time a question of the presence of epidemic encephalitis. One would more readily discount the positive results with encephalitic material were it less rarely possible to demonstrate herpetic virus in the nervous tissues or spinal fluid of non-encephalitic indi-

viduals. I do not feel, however, that a sufficient study has been made of the possible virus content of human nervous tissue, especially the Gasserian ganglia, of non-encephalitic individuals, to permit the conclusion that herpetic virus is more readily demonstrable in encephalitic tissues than in the non-encephalitic.

I cannot agree entirely with Zinsser that "epidemic encephalitis is beyond doubt an infectious disease in which the virus causes lesions in the central nervous system, comparable in histologic principles to those in poliomyelitis and to some extent, to those in rabies." While it may be admitted that the clinical course and even the pathologic histology of encephalitis suggests an infectious etiology, the cerebral lesions, so far as they have been described, are not in my opinion comparable to those of poliomyelitis nor of rabies, and they do not force upon one the conclusion that they are the effect of a filterable virus. Vascular changes, particularly the presence of minute hemorrhages and perivascular infiltrations, are described as the most characteristic features of the histologic picture. Although DaFano has emphasized certain structural changes within the ganglion cells which he has observed, most authors have not found any neuro-cellular alterations which they have regarded as in any way specific. On the other hand in all the filterable virus diseases of the central nervous system it is the changes in the nerve cells themselves which are the most distinctive feature of the lesions. Thus in poliomyelitis there is the necrosis especially of motor ganglion cells, in rabies the intracytoplasmic Negri bodies and cellular necrosis; in experimental herpetic encephalitis of rabbits there are the intranuclear inclusions of Lipschütz. To say that any given lesion, whether in the central nervous system or elsewhere, indicates the activity of a filterable virus, I feel that one must present evidence of some particular or specific effect of such activity upon a certain type of cell. Each filterable virus so far as I am aware seems to act in intimate relation with a certain kind of cell in each of its specific lesions. Consequently I cannot accept the presence of hemorrhages and perivascular infiltrations alone as indicating the activity of a neurotropic filterable virus.

The problem of the etiology of epidemic encephalitis is still unsolved, and at the present time there does not seem to me to be any convincing evidence that it is caused by the herpetic virus.

The contingency of severe herpetic infections of the nervous system of man must be constantly borne in mind however, and the virus sought for in obscure nervous conditions of every sort.

It would seem an easier matter to establish the correct relationship between herpes simplex and herpes zoster or zona in man; but here again there is uncertainty and confusion.

Herpes simplex, as we have already stated, must at present be distinguished from zona. While there are many relative distinctions between them there are only two which seem to me to be of determining importance, namely, that no virus has been transmitted from true zona to lower animals in series, and that an attack of zona frequently seems to confer a substantial immunity (1) (24) (35).

Zona, or shingles, is an eruptive disease, the individual skin lesions of which are indistinguishable histologically from those of herpes simplex, though they are usually more severe and more extensive than the latter. The skin lesion consists of a vesicular eruption upon an erythematous base; it has a special topography which is usually unilateral along the course of distribution of a spinal nerve root. It affects the trunk more frequently than the extremities, though a facial zona is not uncommon.

Frequently zona is accompanied by nervous disturbances, particularly pains which precede and nearly always follow the cutaneous eruption. There is an associated inflammation of the corresponding posterior root ganglion and there may be also an injury to the neighboring portion of the spinal cord. As a rule the disease does not recur.

Although no virus has been found in zona which is transmissible in series to lower animals, Kundratitz claims to have infected successfully two infants, eliciting a local eruption after an incubation period of eleven days.

As with herpes one may recognize two types of zona, namely, the idiopathic which appears out of a clear sky, so to speak, and the symptomatic which may occur apparently secondarily either to an intercurrent infectious disease or to an intoxication.

Herpes simplex and zona merge into each other so completely clinically that it is often impossible to distinguish them without resort to animal inoculation. There is need for further study of this clinical problem. For example one sees reports of recurrent zona, like the

case recently observed by Skoog. Typical zona frequently seems to confer a lasting immunity and it would be of great interest to know if any of the instances of clinical zona which recur are caused by a transmissible virus, that is, a strain of herpes simplex virus.

There is no doubt that herpetic eruptions in man sometimes have a neural distribution, and that they may be associated with inflammatory changes within the corresponding nervous ganglion. Experimentally it is equally certain that the herpetic virus is capable of causing in animals a zonal eruption halfway around the body following a local cutaneous inoculation. Teague and Goodpasture first demonstrated this by increasing the susceptibility of the skin of guinea pigs and rabbits to herpes by coating the skin a few times with coal tar. The application of tar causes an epithelial hyperplasia and a slight inflammation of the epidermis. On inoculating herpetic virus into a small scarified area of the skin thus treated a local lesion results, followed in a few days by a secondary zonal eruption of herpetic vesicles quite comparable to human zona. The virus passes from the skin, evidently by way of the cutaneous nerve filaments, centrally to the posterior root ganglion, thence outward along other nerve filaments to the periphery, where it sets up in the skin secondary local infections manifesting themselves as vesicles. The virus on reaching the posterior root ganglia not only may proceed centrifugally but centripetally as well; and on entering the spinal cord it usually causes a myelitis in the region invaded. Furthermore animals which recover from an experimental zonal herpes are immune to subsequent inoculation. Thus the herpes virus is capable of inducing, in animals at least, a disease which is quite comparable to herpes zoster in man.

While we must continue for the present to classify those instances of human zona in which there is no agent transmissible to lower animals separately from herpetic zosteriform eruptions, in which the agent is transmissible, I am not thoroughly convinced that the two diseases are essentially etiologically distinct. The distinctiveness of the two chief characteristics of zona, namely, non-transmissibility to animals and immunity production, may successively be explained possibly on the basis of variations in virulence of different strains of herpetic virus, and on the extent and duration of the inflammatory lesions. Animal inoculations with herpetic virus have proven the

existence of strains of transmissible virus which vary in their virulence for the rabbit. One strain may cause only a mild keratitis if the cornea is inoculated, another will cause a violent inflammation of the eye and invariably a secondary encephalitis. Also the virulence of a particular strain for man may be greatly diminished or completely lost by frequent passage through the rabbit (39). Immunity following an experimental herpetic eruption is a variable factor. A very small local lesion in the rabbit may cause a slight immunity in a given time; while a more extensive infection, especially with involvement of the central nervous system, confers a very strong immunity. In this connection more evidence is needed as to whether an attack of non-transmissible zona will confer a cutaneous immunity to inoculation with herpes virus. Teissier, Gastonel and Reilly report two cases in which herpes virus was inoculated successfully upon the skin of patients during the evolution of a zonal eruption.

The great frequency of herpetic infections in man leads one to conclude that the herpetic virus is easily transmissible under natural conditions, and that it has an extensive distribution. The wide prevalence of the disease has led to some discussion concerning the origin and dissemination of the virus. Herpetic virus has not been found in the external environment, and Doerr has pointed out that its known properties indicate that it does not survive long outside the human host.

Because labial herpes is the most common clinical type of herpes simplex it seems probable that the virus is spread most commonly by direct contact with active lesions, or through infectious saliva. Several investigators have demonstrated an active virus in the saliva of individuals without herpetic eruption (22), although the saliva apparently is usually virus-free at the time of a labial eruption. According to Flexner and Amoss the frequency of salivary virus carriers is not great. Further it has been shown that the saliva is innocuous in the intereruptive periods in individuals who are subject to recurrent attacks of labial herpes (39). This would indicate that such individuals do not become reinfected from their own saliva. A completely satisfactory explanation therefore of the mechanism of dissemination of the virus has not been found.

The question of the distribution of herpetic virus within the host

following a primary infection has received considerable attention. Bastai and Busacca have maintained that following a primary infection the virus becomes widely distributed throughout the body by means of the blood stream. In support of this contention these investigators claim to have been able to demonstrate, in a large proportion of individuals with the disease, active virus both in the blood and the cerebrospinal fluid. Fisher on the other hand has cast doubt on the accuracy of their methods. His own results and those of others indicate that it is only rarely possible to obtain virus either from the blood or the cerebrospinal fluid.

The frequent outbreaks of herpetic eruptions in the course of certain infectious diseases and especially in association with intoxications of various kinds render it very probable that the virus may reside in a latent form indefinitely in a large proportion of a selected population. Thus Schotmüller was able almost invariably to induce an eruption of labial herpes by injecting into patients a vaccine of dead colon bacilli. The recurrence of herpetic eruptions breaking out in certain individuals at practically the same site time and again, are an evidence of a latency of the virus in intereruptive periods. In such cases Teissier, Gastinel and Reilly, and Nicolau and Poincloux were unable to demonstrate virus in skin after the lesions had healed.

If we except those instances in which virus has been obtained from nervous tissue and the cerebrospinal fluid in cases of epidemic encephalitis, herpetic virus has been demonstrated in individuals free of herpes, in the saliva and rarely in the cerebrospinal fluid. So exceptional is it to find the virus in the cerebrospinal fluid that this medium cannot be thought of as a reservoir for a latent virus in many cases. The salivary virus has been non-infectious for the human skin in the experiments of Teissier, Gastinel and Reilly, and the saliva is usually virus free when an eruption on the lip is present. Consequently it is hardly plausible that recurrent attacks of herpes are dependent upon a virus harbored by the saliva in intereruptive periods.

It is therefore evident that we do not know where the virus resides if it remain latent in intereruptive periods. The results of animal experimentation have given us, however, a rational basis for suspecting that it may be harbored in an inactive state within the nervous tissues, particularly the nerves and the ganglia. It is quite obviously possible

for a person who is the subject of a cutaneous herpes to infect another person by direct contagion provided the virus comes in contact with a susceptible point such as an abrasion on the lips or mucous membrane of the mouth or throat. If the virus first infects the mucous membrane of the mouth anywhere within the distribution of the sensory division of the fifth cranial nerve, experimental evidence demonstrates the possibility that it may invade the local nerve filaments and thus reach the Gasserian ganglion from which later it may proceed outwardly to cause an herpetic eruption somewhere upon the peripheral distribution of this nerve.

Following a primary infection, if invasion of nerves occurs in the human as in lower animals, it seems quite probable that the virus remains in a latent state within the ganglia after the local lesion has healed. A second cutaneous eruption then may result from an auto-infection. This may occur as a result of injury directly to the nerves themselves, as in operations upon the Gasserian ganglion reported by Cushing. In the disturbed physiological states associated with certain infectious diseases and intoxications which predispose to herpetic eruptions there may also be a cellular injury which sets in activity a latent virus.

It has been shown experimentally that herpes is easily inoculable either upon lower animals or upon man by placing the virus in contact with injured epidermal cells. Cellular injury seems to be a most important if not an essential preliminary to a successful primary inoculation, and it may be of equal importance in setting in activity an otherwise latent virus.

It seems to me probable from experimental and clinical facts that herpetic virus does reside in a latent state within the human body and specifically in the nervous tissues, perhaps primarily within nerve cells of the ganglia; and that neural disturbances are frequently the basis of subsequent outbreaks. The occurrence of the virus within the saliva, the blood and the spinal fluid, I think, must be looked upon as accidental. The evidence at hand indicates that a generation or growth of the virus can take place only in intimate relationship with certain cells, and the cells of nervous tissue, in some animals at any rate, is an excellent medium for its proliferation. There is no ground for assuming that the virus can increase in saliva, blood or spinal fluid.

In considering the epidemiology of any virus disease one should bear in mind the possibility of latent infestations not only from the standpoint of the carrier problem, but also from that of endogenous reinfections. Certainly in the case of herpes the possibility of inciting to pathogenic activity a quiescent virus by an intercurrent disease or physiological disturbance is a consideration of importance.

The many facts which lead one to believe that the activity of filterable viruses is intimately associated with certain cells of the host, and the undoubted predisposition of injured cells to become more receptive to many virus infections, should cause one to consider very carefully what tissues might serve as natural portals of entry on the condition that they present susceptible injured cells. In most cases of rabies in the human, for example, this point is clear. Injuries due to the bite of rabid animals expose nervous tissue to contact with virus. Abrasions of the skin expose epithelial cells and nerve filaments to accidental contamination by infectious saliva.

In herpes we find the major portion of eruptions occuring in the peripheral distribution of the sensory division of the fifth cranial nerve. From experimental observations I feel sure that contact infections with herpetic virus occur most commonly through the mucous membranes particularly of the mouth and throat. In genital herpes the portal of entry is in all probability through the mucosa of the urethra. It is in these delicate mucous membranes that one may expect to find most frequently epithelial injuries which may offer a foothold for the virus. Of very great importance in this connection is the possibility that bacterial infections of the mucous membranes often prepare the ground for a subsequent or coincident virus infection by injuring the epithelium. A streptococcal pharyngitis or tonsillitis would offer, it would seem, an ideal nidus for the reception of herpes and perhaps other virus infections. One recalls the intimate association of small-pox virus and the streptococcus. May it not be that these two pathogenic agents complement each other, the streptococcus injuring the epithelium of the pharyngeal mucosa, the variola virus then taking hold upon it as it does after scarification of the skin? The two agents could be transmitted together, the one serving like the artificial procedure of scarification to render epithelial surfaces receptive for the other.

Following an initial infection in the mucous membrane of the mouth, nose or throat we may believe from animal experiments that herpes virus like the rabic and perhaps the poliomyelitic viruses, can invade the nerves supplying the area of local injury. In this way it might readily gain access to the Gasserian ganglia or to the brain. The demonstration by Howard of lesions within these ganglia in association with herpes labialis is evidence that it does enter these structures. Experimental production of an herpetic zosteriform eruption showed us that the virus may not only proceed centripetally along nerves from a local site of infection, but centrifugally as well. If we assume a latent herpetic infection in the Gasserian ganglia the pathogenesis of herpes which occurs on or about the face, is I believe better understandable. In other distributions of herpes and of zona it is necessary to assume a more widely spread invasion of the nervous system by virus. In the case of zona of the trunk the intestinal mucous membrane must be considered as a possible portal of entry for an unknown virus.

In the previous discussion I have referred to herpetic virus as if it were a living infectious agent. Recently Doerr, Naegeli, and others have suggested the hypothesis that this virus may be a transmissible ferment or non-living toxic substance which so acts upon cells as to cause a multiplication of the same ferment or toxic substance, implying that it may arise spontaneously under certain conditions.

While it would seem useless to enter into a discussion as to the distinction between a living thing and a ferment, there is what appears to me an important practical point involved in this theory.

So long as we conceive of virus diseases as infections due to living agents there is the obvious implication of a possibility of identifying these agents morphologically and of cultivating them upon a non-living medium, thus submitting them to a more intensive study. On the other hand, if they are interpreted to be reproduced only through the action of living cells of the host, it would seem useless to continue efforts in the direction of cultivation on a lifeless medium. The group of virus diseases is at present too ill-defined and too heterogenous to warrant the wide acceptance of any generalization which would tend to inhibit investigation of them from any direction.

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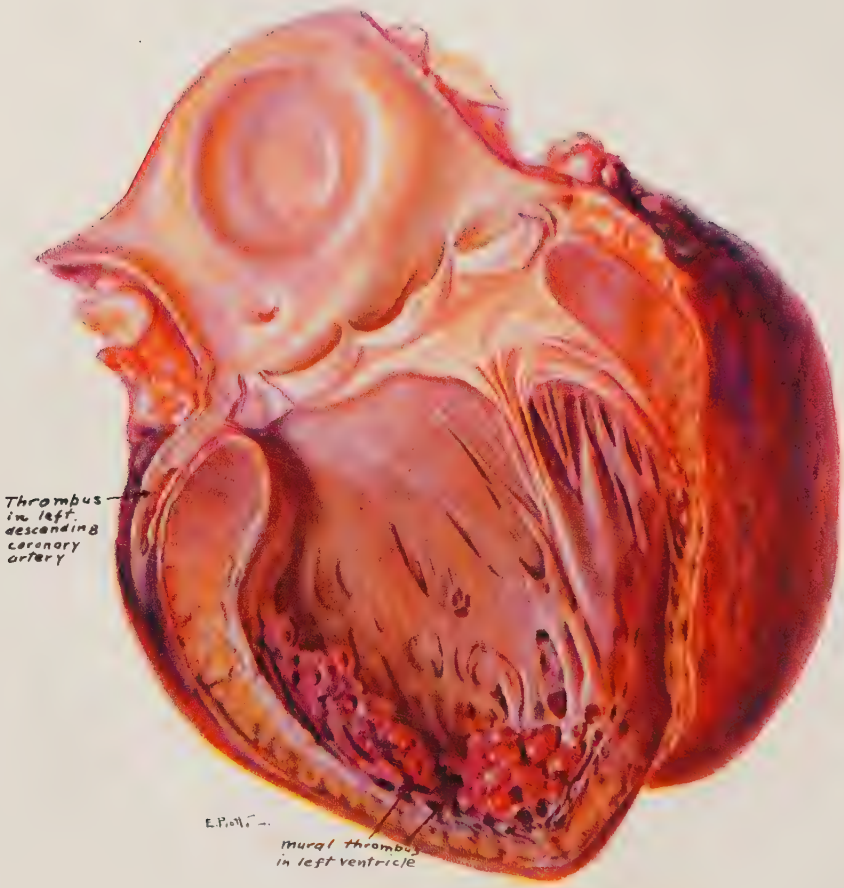

This Drawing of Case 141 (Fig. 32) Shows the Characteristic Thrombus Lodged in the Left Descending Coronary Artery and the Large Mural Thrombus in the Left Ventricle

The point of rupture of the heart is not shown here. (Drawing obtained through the courtesy of Dr. J. P. O'Hare.)

CORONARY THROMBOSIS: ITS VARIOUS CLINICAL FEATURES

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I. GENERAL CONSIDERATIONS AND HISTORICAL REVIEW

The historical development of our knowledge concerning the clinical recognition of coronary thrombosis forms an interesting chapter of modern internal medicine. As we shall see, despite the fact that the condition is now one that in most cases can be readily diagnosed, it is only in very recent years that its distinctive features have been properly understood and differentiated from those that pertained to allied but decidedly different morbid states. In this review no attempt was made to analyze all the previous contributions that bear on the present discussion, but rather to pick out some here and there that were considered to be significant or helpful in one way or another, and which formed the various steps in the development of a clinical picture, now quite discrete, but which as recently as twenty years ago was entirely unrecognized. Incidentally the bulk of our knowledge has come through the careful observations of practising clinicians together with the usual examinations of their post-mortem material rather than by any of the more complicated processes of experimental investigation.

For a great many years both clinicians and pathologists were observing isolated instances of rupture of the heart, aneurysm of the ventricles, occlusion of the coronary arteries and myomalacia. Looking through these records one is struck by the fact that they were regarded in the light of interesting pathological processes, but as having no great clinical value because they were thought to be impossible of recognition during life. In fact, it was not generally appreciated that occlusion of the coronary artery could be compatible with a fair degree of health. It will also become evident from such a review that what we all now recognize as cases of acute coronary thrombosis were generally regarded as instances of severe angina pectoris or status anginosus. It is this distinction between attacks of angina pectoris and attacks of coronary thrombosis that is a development of the past 15 years or so. In fact, our great teachers until a few years ago confused these two conditions, merely regarding one as a more severe form of the other. This was true of Sir William Osler in his Lumleian Lectures (1). Here, in a discussion of angina pectoris, cases were divided into three types, i.e., the mildest, mild

and severe. It seems clear to the reader that amongst the severe forms were included cases of coronary thrombosis, and Osler noted the frequent finding of coronary thrombosis with the sequellae of pericariditis and rupture of the ventricle in the autopsy material of his cases. There was no indication, however, that a clinical ante-mortem differentiation was being made between the condition we now recognize as coronary thrombosis, no matter how mild the pain may be, and angina pectoris. The same may be said about the writings of Sir James Mackenzie, for in his last work on Angina Pectoris, published in 1924 (2), it is apparent that he had not made clinical diagnoses of coronary thrombosis in his practice.

Two other names that are intimately associated with the literature on coronary artery disease are Krehl and Huchard. The former called attention to the possibility of recovery after an attack of coronary thrombosis (3). He also discussed the development of aneurysms of the ventricle and thought they were a not infrequent cause of rupture of the heart. As will be shown below, rupture of the ventricles occurs much more commonly during the early days following coronary thrombosis long before there is opportunity for true aneurysmal formation. He did call attention to the fact that the symptoms were much more likely to be severe if the vessels were occluded suddenly than when the sclerosis of the coronary artery was more diffuse and gradual in its development. Huchard in a pathological analysis of 185 fatal cases of angina pectoris (4) called attention to the importance of the coronary artery and to the frequency of coronary thrombosis, but this type of retrospective study did not furnish the clinician with the critical bedside data which might enable him to diagnose the condition during life. Dock (5) was one of the very first to report an instance of coronary thrombosis diagnosed ante-mortem and proved at autopsy. He recognized the importance of the pericardial friction rub as an aid in diagnosis. At the time of his publication one would judge from the account it contains that the other important features that make up the clinical picture of coronary thrombosis were not thoroughly known; at least, it is surprising that further papers did not appear by the same author to emphasize the importance of recognizing this clinical entity.

The first important and satisfactory account of the clinical features

attending attacks of coronary thrombosis was published by Obratzow and Straschesko (6). These Russian authors diagnosed correctly two of the three cases they published. They emphasized a triad of symptoms,—severe lasting retrosternal pain, dyspnoea and orthopnea, and finally gastralgia. All three of their cases had precedent angina pectoris. They called attention to many of the features we now recognize as important findings in coronary thrombosis, e.g., gallop rhythm, Cheyne-Stokes breathing, pericardial friction, distant heart sounds, mural thrombi, pale cyanosis, etc. They also noted the different clinical and pathological events that might result depending upon the size of the coronary artery involved. They indicated that softening and rupture of the infarcted area might result with hemopericardium. They ascribed the fever that was present in their second case to pericarditis and pleuritis. It is surprising that after such a splendid publication appearing in the German literature, the condition was not more quickly appreciated on the continent, although in the following year a similar report of four cases, of which two were diagnosed ante-mortem, was published by Hochhaus (7).

During the past 15 years physicians in America have added much to our knowledge concerning this condition. We owe a great deal to the careful observations and the persistent efforts of Herrick, who first really focussed the attention of the American medical profession on this disease. In 1912 he emphasized the fact that coronary thrombosis was a clinical entity, could be recognized during life and that it need not end fatally (8). Curiously enough this publication did not produce the desired effect for it aroused no interest. After a lapse of five or six years further papers appeared by Herrick and his associates (9, 10, 11), in which the matter was again taken up. In fact, that same year Levine and Tranter (12) published a report of two cases of coronary thrombosis, one of which was diagnosed ante-mortem, although at that time they were entirely unaware of Herrick's previous work. During these years it is quite clear that Libman (13) had been familiar with coronary thrombosis as a condition differing from ordinary attacks of angina pectoris. In 1916, while discussing the various kinds of chest pain, he mentioned in passing "the diagnosis of a recent thrombosis could often be facilitated by the development of a slight temperature, moderate leucocytosis and evidence of a patch

of pericarditis, all coming on within a couple of days after the attack of severe pain" (14). There were no case records published at this time. The first to call direct attention to the development of fever and leucocytosis as a part of the picture of coronary thrombosis were Levine and Tranter (12). They also pointed out that when the pain was localized in the epigastrium this association of fever and leucocytosis together with other features might strongly simulate an acute surgical upper abdominal condition. One of their two cases was operated on by mistake as an acute surgical emergency, and the other was just saved from this unnecessary error by proper ante-mortem diagnosis. Further attention was called shortly afterwards to this relation between heart disease, surgical operations and conditions that simulated acute surgical emergencies (15, 16).

Shortly after these publications an extensive literature appeared emphasizing again and again many of the same points that had previously been noted. Amongst the more important article of a clinical nature were those by Gorham (17), Paullin (18), Levine (19), Longcope (20), Thayer (21), Wearn (22), Gordinier (23), Hamman (24), Benson (25) and Wolf and White (26). These various publications served to bring the clinical features that are diagnostic of coronary thrombosis before the medical public in this country, so that now as Christian (27) has stated, it is an easily diagnosable disease. Some of the above authors emphasized particular points that lead the way for a clearer understanding of the entire subject. Gorham (17) pointed out the diagnostic importance and frequency of a pericardial friction rub, while Wearn (22) besides giving a very clear description of the symptoms and signs of the disease, called attention to a marked diminution in the height of the waves in the electrocardiograms in a few of his cases. Levine (28) brought out the interesting observation that those patients who had hypertension and angina pectoris before the attack of coronary thrombosis might become free from anginal attacks if recovery was attended by a permanent and distinct lowering of the blood pressure. This was found to be true in many of the cases that had the most satisfactory type of recovery.

While this extensive literature was appearing in America it is surprising that it was not until 1925 that this subject of coronary thrombosis as a specific problem began to be considered in England. Allbutt

(29), however, many years before had called attention to the pathological condition, not from the point of view of clinical recognition, but rather in so far as it affected his theory of the aortic origin of angina pectoris. Mackenzie (2), as has been mentioned above, never made the clinical distinction between angina pectoris and coronary thrombosis, although he contested Allbutt's aortic theory and maintained the importance of the blood supply of the heart in the mechanism of the attacks. Only in the past two or three years have British authors become aware of this problem. This is shown in the appearance of several recent publications on this subject by McNee (30), Gibson (31), and Parkinson and Bedford (32). The same development was going on in France. Despite the splendid pathological study of Marie (33), in which the post-mortem changes of coronary thrombosis were well described, no clear association of this process with a definite clinical symptomatology was appreciated until many years later. Recently publications have appeared from that country dealing with the clinical aspects of the disease similar to those in other countries (34, 35, 36).

A most important and helpful advance in the clinical recognition of coronary thrombosis came about in this country when certain electrocardiographic changes were found to be fairly characteristic of the acute stages of this condition. This work was the development of some experimental observations in dogs done by Smith while he was associated with Herrick who at this time was making some similar clinical observations. Smith (37, 38) noted sharp inversion of the T wave of the electrocardiogram in dogs shortly after the coronary arteries were ligated. At about this time Herrick (11) published an account of the first case of coronary thrombosis which was proved by post-mortem examination, with electrocardiograms showing sharp inversion of the T waves in leads one and two, which were not unlike those obtained by Smith in his ligation experiments. He also noted that the T waves were less negative 10 days later, and in five months the tracings showed curves of low amplitude. At this time the more characteristic changes that are found in human electrocardiograms during the first few days after an attack of coronary thrombosis were not fully appreciated but the above work served as a forerunner of the contributions that followed.

The discovery by Pardee (37) that during the early days following an attack of coronary thrombosis there are fairly characteristic changes in the electrocardiograms has proved to be a most valuable addition to our methods of diagnosis. As will be seen in some of our case histories, there are instances in which this electrocardiographic sign may be the single definite evidence that distinguishes the condition and that differentiates it from other entirely unrelated possibilities like gall stones or gastric ulcer. These changes were described as consisting of a high take-off of the T wave from the descending limb of the R wave. This alteration does away with the customary isoelectric interval that normally is found between the R and T waves. It was also noted that the T wave goes through rapid changes during subsequent days after the attack and may become sharply inverted. This publication was soon followed by others which confirmed and somewhat elaborated the electrocardiographic evidence of coronary artery disease (40, 41, 42, 43, 44, 45, 46, 47). One of these (44) is worthy of particular attention because the authors found the characteristic changes in the R-T interval as soon as six and one-half hours after the onset of the attack.

It is the purpose of this paper to review the various clinical features of coronary thrombosis including the electrocardiographic changes, rehearsing the typical events of acute attacks which now are quite well established, discussing certain atypical forms and complications, and finally considering the therapeutic problems involved, for very little has been written in the past about therapy.

The data upon which this study is based includes 145 cases, slightly less than half of which were seen at the Peter Bent Brigham Hospital, and the others in private consultation practice. Some of the cases were previously reported for other purposes, first (12) to call attention to the group that resemble acute surgical conditions of the abdomen, secondly (19) to present the clinical features of the typical acute attack, and thirdly (28) to emphasize the fact that satisfactory recovery from such a condition may take place. There have been numerous additional data that have come to light more recently that made it valuable to collect all our information and thereby to make a more complete review of the entire subject. Only cases that have been proved by autopsy or that have been so clear-cut that little

doubt can exist as to the accuracy of the diagnosis have been included in this study. In most of the fatal cases, accurate ante-mortem diagnoses were made.

II. ETIOLOGICAL FACTORS

There is no one specific disease that is a frequent percursor or that is in any intimate way a causative factor in the production of coronary sclerosis and thrombosis. The common infectious diseases seem to play no rôle whatever, in fact the contrary is nearer the truth, i.e., these patients have had very few of the common illnesses. Furthermore, there is no evidence whatever pointing to any close relationship between foci of infection and coronary disease. It has often been suggested that the actual acute thrombosis of the coronary artery may be precipitated by an acute infection but we find no reliable evidence to substantiate this view. The fever and leucocytosis that is associated with coronary thrombosis as we shall point out later, follows rather than precedes the attack.

a. Relation to angina pectoris

It is generally true that coronary thrombosis is the end result of previous angina pectoris. In this sense many considerations that pertain to the one also hold for the other condition. Often the patient, and even the physician, is unaware of the previous existence of angina pectoris, for the complaint may have seemed trivial and of insufficient importance to call for any attention. In many of the cases where the attack of coronary thrombosis seemed to have been the first indication of any existing heart disease, we have found by close questioning that for some months or years there was definite constriction in the chest on hurrying, or some other significant complaints. Some cases were too sick to permit obtaining an accurate history, but on the whole it is safe to say that the great majority of patients had definite angina pectoris antedating the attack. There were, however, a much smaller number in whom no such history could be obtained even after the most careful inquiry. In fact, some would have been considered to be in perfectly normal health in every way until this most serious spell occurred. In these, after recovery has occurred, angina may be present, i.e., an attack of coronary thrombosis may initiate a typical course of angina pectoris.

b. Diabetes

A condition that is intimately related to arterial disease and which has a most important bearing on the development of coronary thrombosis is diabetes. In an earlier article (19) it was pointed out that about 7 per cent of patients with angina pectoris had previous well defined diabetes. In this group of 145 cases there were 34 or 23.7 per cent in whom glycosuria was found, or where it was definitely known that diabetes had existed previously.

These figures are only approximate, as in eight of the cases a slight amount of sugar was present in the urine as a transient phenomenon during the early days of the attack. In others this amount, although readily disappearing during convalescence without any particular treatment for diabetes, was quite considerable, reaching as much as 2 per cent. In some instances, it was definitely known that the patients had had diabetes for years but had controlled the glycosuria by dietary measures and during the attack of coronary thrombosis showed no sugar in the urine or only slight traces. It seems likely, however, that the attack of coronary thrombosis, possibly because of the great pain and fear that accompanies it, produces by itself a glycosuria that need not be indicative of diabetes, as a fair number of patients gave no evidence of diabetes upon recovery, although they showed a distinct glycosuria during the attack. Notwithstanding these diverging factors, it has been striking to find so many diabetics in this group, and we feel that among the distinct disease entities that are etiologically related to coronary thrombosis, diabetes is second in importance only to a previously existing hypertension.

The presence of sugar in the urine or a previous history of diabetes did not alter the age at which coronary thrombosis occurred. The average age of the diabetic group was 58.1 years, and that of the entire series was 57.8 years. It might have been suspected that a group of diabetics would develop coronary disease earlier in life than non-diabetics, but that was not so. It must be appreciated, however, that the type of diabetes included here really comprises the mild form occurring in the second half of life. Diabetes, moreover, only slightly affected the prognosis, for 67 out of 143 of the entire series were known to recover from the immediate effects of the attack, or 46.8

per cent, with a mortality of 53.2 per cent, whereas the immediate mortality of the diabetic group was 58.8 per cent. There was a larger proportion of females in the diabetic group than in the non-diabetic. Of the 34 diabetics, 12, or more than one-third, were females, whereas of the 111 non-diabetics, only 22 were females, or one-fifth.

The relationship between diabetes and coronary disease needs particular emphasis. Since the great improvement in the treatment of diabetes that followed the discovery of insulin, new problems in the care of diabetics have arisen. The incidence of fatal diabetic coma has diminished strikingly, surgical complications are more readily cared for, and possibly because diabetics are now able to live longer than previously, the problem of vascular disease in diabetes, which can only develop over a span of years, has proportionately grown tremendously. Fitz and Murphy (48) very recently called attention to the great frequency with which diabetics died of vascular disease. This is particularly true of diabetic patients over 35 or 40 years old, at an age when the diabetes is not particularly severe. In the care of such patients the problem of angina pectoris often becomes of much greater importance than that of diabetes, and proper treatment must be essentially directed with this point of view in mind. The fact that the presence of diabetes did not alter the prognosis of the attacks of coronary thrombosis nor the age at which they occurred, leads one to feel that it had no causative influence in the disease of the coronary arteries but merely indicated the type of person who had a vulnerable vascular system.

c. Hypertension and arteriosclerosis

A previously existing hypertension is probably the most common single etiological factor in the development of coronary thrombosis. Here, as well as in some other considerations, exact data are difficult to obtain. In many instances the patient did not know whether he had a previous hypertension. Often, although they were entirely symptom free, it was discovered that at some earlier time, such as during an insurance examination, the blood pressure was elevated. In other cases, although at the time of the attack the blood pressure readings were normal or low, as a result of finding well marked evidence of retinal sclerosis, it was quite evident that a previous hypertension

had existed. Finally in some patients hypertension developed a few days or a week after the onset of the attack which indicated that it had been present before but had temporarily fallen. There were, however, a sufficient number of patients, in whom it was known that at no time had there been an elevated blood pressure, to make it clear that hypertension is not an absolute prerequisite.

In this series, 58 patients were known to have had hypertension. This included all cases with a systolic reading of 160 or over, or a diastolic pressure of over 100. The average pressure of this group was 191 mm. systolic and 110 mm. diastolic. The average age of this group was 58.5 years, which is essentially the same as that of the entire series. There were 39 males and 19 females, indicating a distinctly larger proportion of females than in the whole group (111 to 34). The inference from this is that a previous hypertension is more apt to be found in the female cases than in the male and that it is comparatively more rare to find a woman with a known antecedent normal pressure than a man. Hypertension did not affect the immediate prognosis, as of the 58 in this group 28 were known to have recovered and 29 died. (In one case the outcome was not known.) This is possibly slightly better than the average of the entire series.

It was definitely known that only six patients had blood pressure readings within normal limits previous to the attack of coronary thrombosis. No doubt some of the others in the unknown group had normal readings. Of course, all of the latter group, and most of the hypertensive group, had normal or low readings after the onset of the attack. Many patients with normal blood pressures showed retinal sclerosis of a sufficiently well marked degree to indicate that a previous hypertension had existed. The changes in blood pressure that occurred with the attack will be taken up below, but at this time it may be pointed out that a distinct hypertension existed as a forerunner of coronary thrombosis in the majority of cases.

Inasmuch as coronary thrombosis is essentially a disease of the arteries, it is a matter of some moment as to what evidence there is of sclerosis in other parts of the arterial system. No accurate estimate of radial or brachial sclerosis was made in this study because of the difficulty of interpreting variations from the normal. Considering that the average age of this group is 57.8 years, peripheral arterial scerlosis

of some degree can be regarded as normal. In general it was found that most of the patients showed some sclerosis of the radial, brachial and temporal arteries, some of an unusual degree, but a moderate number only to a slight degree. There were others in whom no sclerosis could be made out. The frequent finding of hypertension, however, indicated that small blood vessel sclerosis was going on in most of these patients. Other evidences of arterial disease was the common history of intermittent claudication that appeared in these patients, and the occasional occurrence of hemiplegia, and the like. Although disease of the coronary arteries is often only a part of generalized arteriosclerosis, there are large numbers of individuals in whom very little evidence of arterial disease can be found anywhere in the body, except for this one important focus.

d. Syphilis

Syphilis is rarely an underlying factor in the causation of coronary thrombosis. In only three of the 89 cases in which a Wassermann test was done was the reaction positive, and in one other, although the Wassermann was negative, a definite history of a primary infection was obtained. This would indicate that 4.5 per cent of the patients were syphilitic. It does not follow that even in these syphilis had a direct causative influence in the coronary thrombosis. That it was so of the patient aged 36 who was the youngest in the series seems likely, but it may well be true that in the others the luetic feature was incidental. The average age of the three who had a positive Wassermann was 45 years, which is 13 years less than the general average. Certainly it may be stated that syphilis is not a common cause of coronary thrombosis, and when it is the disease can develop at a somewhat earlier age than the general average. There is no evidence from this small group that syphilis alters the prognosis, for two of the four cases recovered and the other two died.

e. Other diseases

Rheumatic infections, which are the most common specific cause of serious heart disease, are of no importance in the condition here considered. Only three patients of the series had a past history of rheumatic fever and those attacks occurred 33, 49 and 60 years before

death from infarct of the heart. Post-mortem examination in each case showed no disease of the valves, and in no way did it seem that this previous rheumatic infection had any causative relationship to the coronary thrombosis that was found. In fact it may be said that not only do patients suffering from coronary disease have no history of rheumatic fever, but that those having rheumatic heart disease but rarely show coronary disease.[1] This probably is true even of those younger rheumatic patients having aortic insufficiency who may have attacks of angina pectoris.

It is apparent that those conditions which predispose the individual to early arterial disease might be of some importance in the etiology of coronary thrombosis. It is, therefore, surprising that a history of gout was found in only one case. It is likely that if that factor had been investigated more critically other instances would have been found. In a series of 103 patients with angina pectoris (19), five were known to have had gout. This is of interest in the present discussion because the etiological factors of angina pectoris and of coronary thrombosis are probably much the same.[2]

f. Heredity, physical type, work and weight

It follows from the foregoing discussion that specific diseases, except diabetes and hypertension, play an unimportant rôle as a causative factor in the development of coronary thrombosis. Heredity, on the other hand, is of considerable importance in the etiology of this disease. A large number of the patients here discussed have family histories indicating great susceptibility of the vascular system to degnerative disease. With this, or more likely as a part of the inherited traits, there is frequently a characteristic type of constitution that patients with coronary disease manifest. The typical patient is a well set person, somewhat over weight, often of considerable physical strength who enjoyed unusual good health. Such patients often have indulged in vigorous physical effort either in the form of

[1] Very recently one of us attended the first case of mitral stenosis and definite coronary thrombosis that has come under observation. This patient recovered.

[2] Since this review was made we have seen three patients with coronary thrombosis who were also suffering from Buerger's disease. Two of these were comparatively young, 36 and 38 years of age.

sports or in their ordinary work, and when they have not they were apt to feel that they had more than the average physical strength even if they were not accustomed to use it. To be sure, etiological considerations in general do not apply with as equal force, when discussing degenerative vascular disease in elderly patients such as those over 70 as in younger ones. For in old age it would not be surprising that a thin patient with no striking family history of vascular disease and no antecedent diabetic state should develop coronary thrombosis. It is more logical to conclude that just because of the absence of the predisposing causes, the degenerative process in the arteries which is going on insidiously in all of us was so long delayed. No accurate figures were obtained in this study as to the exact frequency of a family history of coronary or vascular disease. This would require a painstaking inquiry into all the details of longevity and diseases of the relatives of the patients, which was not done. Suffice it to note that after a considerable experience with this condition it is amazing how frequently one finds various members of the same family suffering from early vascular hypertension or coronary disease. One of us has personally seen two of three brothers, all three of whom died of coronary thrombosis at about the age of 55.

In considering the effect of physical work on the development of coronary thrombosis, it seems almost impossible to obtain accurate data. We are at present dependent on general impressions. There are certain features which indicate that physical effort is conducive to early disease of the coronary arteries. Many of the patients in this group were muscular and strong and had done hard physical work either in their occupations or at play. We all know that the minor attacks of the precedent angina are generally precipitated by effort. We have been impressed by the fact that athletes seem to succumb to vascular disease at surprisingly early years of adult life. These are general reflections despite the abundant evidence recently obtained which shows that there are no immediate harmful effects on the heart from violent effort. The question may be regarded in the light of a mechanical engine which cannot deteriorate through disuse (for the heart is always contracting anyway) but the life of which will be shorter the more it is used. This is not unlike the general conclusion Raymond Pearl came to in studying fruit flies when he stated that "in general,

the duration of life varies inversely as the rate of energy expenditure during its continuance." Concerning mental tension, here again accurate data are lacking but it is our impression it is only of minor importance in coronary disease.

The body weight of patients is of some importance in considering etiologic factors. It has been quite striking to us that coronary thrombosis does not commonly occur in thin individuals. After the age of 40 it is now well known that vascular disease of one kind or another is the most frequent cause of death, and in this connection disease of the coronary arteries plays no insignificant rôle. Recently (49) it has been shown by statistics compiled by insurance companies that those who are accepted as normal risks at the ages of 40 or over, who are 20 to 40 per cent over weight have an increased mortality of 30 to 80 per cent respectively in the following decades. A likely deduction from this, and one that has not at all been sufficiently emphasized, is that if the above is true, and these data are ample and reliable, then those who are under weight and well at 40 probably have even a better expectancy than the average normal. This again, would fit in with the clinical impression that whereas vascular disease of one kind or another is by far the most common cause of death in people over 40, and thin people are less apt to develop vascular disease, the thin have a decided advantage from the point of view of longevity.

g. Age and sex

Coronary thrombosis occurs with greatest frequency, as one would expect, during the latter years of life. The average age of the entire 145 cases in this series was 57.8 years. The largest number of cases, however, occurred in the seventh decade between the ages of 60 and 69. There were 55 such cases, while there were 44 occurring in the previous decade between the ages of 50 and 59 years. This means that 99 or 68.3 per cent were included in these two decades. There were only three cases in patients under 40 years and only one, 80 years or older. There are very rare instances of coronary thrombosis occurring in individuals under 30. One would have reason to suspect syphilis as the etiological factor when the disease occurs in such early years. The average age of the males was 57.4 years, whereas that

of the females was 59.2. We see that the age range covers a long period, from middle adult life to old age.

Age distribution

DECADES	NUMBER OF CASES
30–39	3
40–49	29
50–59	44
60–69	55
70–79	13
80 plus	1
Total	145

The sex distribution of the incidence of this disease is most striking. There were 111 males and 34 females, a ratio of almost three and one-half to one. This is particularly impressive when one appreciates that essential hypertension, which is a frequent precursor of coronary thrombosis, occurs more commonly in women than in men. It is difficult to explain the great frequency of coronary disease in the male. One might ascribe it to the greater amount of physical work that men do, although some might question this and maintain that the humble housewife does just as much work in her home as the men do at their respective occupations. Another factor that may be mentioned is the possible rôle of tobacco. There is considerable difference of opinion as to whether tobacco has any deleterious effect on the heart and particularly whether it is responsible in any way for the development of coronary disease. At present no satisfactory answer to this question is available, but certainly the consumption of tobacco has been in the past almost entirely confined to men and has been one of the few acquired differences in habit between the two sexes. It is therefore logical to suspect this habit of playing some possible rôle in producing such a male predominance in susceptibility to this disease. A more definite answer may be apparent before long if the coming generation of women continue the smoking habit that seems to have become so general. A final consideration in the predominance of males is linked up with the general physique and strength of the males as contrasted to the females. The former are stronger and are more apt to use that strength in sports apart from their work. The

development of coronary disease may be related to this factor in a manner similar to that discussed in the previous section.

III. THE SYMPTOMS AND SIGNS OF CORONARY THROMBOSIS

a. The typical clinical picture and its pathological background

The events that occur when a patient is stricken with an attack of coronary thrombosis have only recently been emphasized. The clinical picture was not described in current text books of medicine until the last few years. It is, therefore, appropriate at this point to rehearse the symptoms and findings of a typical attack before taking up those features that are less constant but none the less important. The patient generally has had a previous story of angina pectoris. This may have manifested itself in its characteristic form and have led him to seek medical advice. Frequently, however, the complaints were regarded lightly by the patient so that no attention at all was paid to them or they were misinterpreted by the physician because of lack of knowledge of this disease. In many instances where coronary thrombosis existed and was supposed to have occurred as the first indication of any disease of the coronary arteries we were able to uncover, by appropriate questioning, a definite history of angina pectoris that antedated the attack of thrombosis by months or years. Rarely, however, it was impossible to elicit any evidence whatever of serious disease of the cardiovascular apparatus preceding such an attack (see cases 54, 104 and 107).

The attack of coronary thrombosis, unlike the typical anginal attack, often is not precipitated by effort. It frequently occurs during rest, while sitting quietly in a chair at a dinner table or during sleep. To be sure, ordinary or more unusual effort is also often found to be a precipitating factor. When the attack takes place the patient is generally quickly aware that something terrible is happening. If he previously experienced anginal attacks he knows that this is different from anything that he formerly has had, or if a patient recovers from one or more attacks of coronary thrombosis he well recalls these spells and the very dates when they occurred.

From the moment the attack has begun until a period of several weeks has elapsed, death may occur at any time as a result of a great

variety of causes. This will become clear as different complications are discussed. The physician very rarely sees those who die instantly. They become problems for the coroner who has long been familiar with coronary disease as a cause of sudden death. If death is not instantaneous we learn that the patient is taken with a severe pain, generally in the chest, although not infrequently in the upper abdomen. The pain is constricting or squeezing in character, and may radiate in the customary fashion to the neck, throat, shoulder, back or arms, more often to the left than to the right. The attack may be collapsing in character. Occasionally the patient actually falls, may become unconscious but more frequently has a sense of extreme weakness.

There frequently is vomiting at the onset of the attack, and it is this feature and the general feeling of distress that makes the patient, the family and the physician believe that the attack is one of actute indigestion, a term that should be given up entirely in medical nomenclature, especially when it ends fatally, for then it practically always is incorrectly used to describe an attack of coronary thrombosis.

Shortly after the attack has begun the patient presents the picture of one suffering terrifically and seems to be in shock. He looks pale, is cold, and the skin has a moist ashen gray color. The pulse will be found to be of small volume and rapid. There generally has occurred a fall in blood pressure and this may continue to fall for several hours or during the subsequent days. Both the fall in pressure and the rise in heart rate are in marked contrast to what happens during an attack of angina when the blood pressure is apt to rise and the pulse rate remains essentially unchanged. In a small number of instances the pulse may remain slow at the start and begin to rise after several hours or on the following day or so. Changes in the blood pressure may likewise be delayed. Sometimes very quickly or at other times only slowly, oedema of the lungs may develop. Occasionally the presenting feature is a patient with acute pulmonary oedema. In most instances a moderate number of moist râles can be heard at the bases of the lungs. In a short while the liver may become slightly enlarged from congestion and tender to pressure. In fact, at times the upper abdomen has a board-like rigidity similar to that which is seen in surgical conditions. At this time the only striking feature in

examination of the heart is the quality of the sounds which become very weak. This is especially true of the first heart sound as heard at the apex, which becomes very faint and at times actually inaudible. Very commonly there is a distinct gallop rhythm and an alternating pulse.

During the course of the first day or two several important developments occur. The pain gradually diminishes though the patient complains of feeling weak. There may have been actual shortness of breath, and at times Cheyne-Stokes breathing is noted. In most cases a slight fever develops. This can easily be overlooked as the mouth temperature may be normal or even subnormal while the rectal temperature may register 100° or 101°F. (case 95). This discrepancy between the mouth and rectal temperature is probably dependent on the state of shock and dyspnea that is present. The skin and mucous membranes may actually feel cold while a true fever is present. At the same time a slight or a marked leucocytosis is apt to be found. Both of these features are probably dependent on the degree of infarction of the heart muscle and very likely represent a constitutional reaction to infarcted tissue. In a similar manner, sterile infarcts in other parts of the body, such as the spleen or kidney, even when unassociated with infection, are generally accompanied by fever and leucocytosis. The fever and leucocytosis in coronary thrombosis can develop as soon as several hours after the attack and thereby can be helpful in early diagnosis.

During this time the patient's general condition and appearance may have changed very little. Those who early develop marked pulmonary oedema, within a day or so will have shown a striking improvement. Some, as we shall see later, develop increasing evidence of failing circulation, such as oedema of the legs and liver. Most, however, show very little of importance except as mentioned above. Twenty of the 145 cases studied developed a pericardial friction rub during the early days and when this finding is discovered it aids greatly in making the proper clinical diagnosis. The exact incidence of a pericarditis and the typical friction rub is no doubt higher than this figure. It will be more often heard the more closely the heart is examined, but that does not mean that even most of these patients need show this sign. It will in some measure depend on the site and

extent of the heart muscle involved. The fever and leucocytosis gradually disappear after several days and in some instances the patient looks and feels perfectly well. Even under such apparently favorable circumstances, the outlook may yet be grave as death can come very suddenly.

In order clearly to understand the events that are taking place, it is essential at this point briefly to recall the pathological changes that are going on in the heart. That portion of the ventricles which was supplied by the thrombosed coronary artery (it is almost always the descending branch of the left coronary) has become infarcted. The process of necrosis may extend outward and involve the pericardium. If this happens, and if it occurs over the anterior portion of the heart, a pericardial friction sound may be heard. If it involves the interventricular septum or the lower or posterior part of the ventricle, even if a localized pericarditis develops, no friction rub need be audible. When the septum is involved, various degrees of heart block may result from the injury to the conduction tissue. Likewise the degenerative changes may progress towards the endocardium. If this occurs a local mural thrombus forms which sometimes reaches a considerable size. The ventricular wall that is infarcted manifests the customary changes seen in injured tissue. Inasmuch as the coronary arteries are not end arteries, an attempt at repair is made by anastomosis and new blood vessel formation. The necrotic tissue may soften and some days after the onset, rupture of the heart may occur with instant death. This was found to be the cause of death in nine of the 46 cases that came to autopsy. In these instances an actual tear was found in the heart, and the pericardial cavity was filled with blood. When the reparative process is sufficient, firm scar tissue replaces the necrotic area and recovery may be complete. In other instances, although healing takes place, it is accompanied by a weakening of the part of the wall involved, and a localized aneurysm of the ventricle results (cases 16, 28 and 50). Finally, from the mural thrombus that formed within the cavity of the ventricle, not infrequently bits of emboli may become free and lodge in distal blood vessels. This is apt to occur after the first week and accounts for instances of sudden hemiplegia (case 74) or infarcts of the kidney (case 39), spleen (case 13) and limbs (case 136). From the above it

follows that there are a train of complications that may arise, all of which owe their origin directly to the infarction of the heart.

In an uncomplicated case after the pain has subsided the patient remains weak, but an uneventful recovery takes place. The temperature and leucocytosis gradually disappear after a variable number of days. The pulse slowly returns to a normal rate and the blood pressure, which had fallen with the attack, frequently remains low permanently, although it rises somewhat from the extreme levels that obtained during the early days. In others the blood pressure again becomes elevated. The various types of irregularities of the heart which will be discussed later, all disappear as well as the evidence of slight circulatory congestion, such as râles in the lungs and tenderness of the liver. The time for the apparently normal state to be resumed varies in different patients from a day or two to a few weeks, depending on the severity of the injury.

At any time after the onset a great variety of complications may develop of which a more detailed discussion will be taken up below. Whereas very little in the nature of treatment is necessary for those patients whose course is simple, much will depend on the proper recognition of the complications and the intelligent treatment of them. It must also be borne in mind that although most of the cases do not present the picture that is generally seen in serious congestive heart failure, i.e., marked pitting oedema of the legs, ascites, hydrothorax, etc., yet some of the atypical cases have these signs and need treatment directed at them.

The physical signs that are present are in most cases of no particular significance, except for the general appearance of the patient, and this is of great importance. He presents the picture of agitation and shock. He gives evidence of extreme pain and apprehension. The skin is cold, moist, pale and has a peculiar ashen appearance. There may be slight or marked cyanosis of the skin and lips. He is apt to be restless and even thrash around seeking relief. Sometimes the pain is so extreme that the patient will actually be tearing the flesh of his chest in the attempt to drag out the demon that is crushing him.

On examination, the heart beat will be found so weak that no visible or palpable apex impulse can be felt in the majority of cases. In some the apex beat will be made out definitely, and it is then apt to

be found beyond the left nipple line. The rhythm of the heart will be dominantly regular in practically all the cases, although after the onset of the attack almost any type of irregularity may come and go, This question will be discussed in greater detail later. In almost half of the cases a slight or moderately loud systolic murmur can be heard, and very rarely an aortic diastolic murmur. This latter finding was present in only one case of this entire series and he had aortic stenosis and insufficiency. There was not a single instance of mitral stenosis in this group.[1] In about one-half of the cases no murmur whatever could be heard.

A point in the heart examination that is much more important than the presence or absence of murmurs is the quality of the heart sounds. The sounds are almost always muffled or distant. This is particularly true of the first heart sound at the apex. On several occasions it was actually found absent, while a distinct second sound could be heard. Occasionally neither heart sounds can be heard over the precordium, though when this is true it is apt to be due to the noisy breath sounds that overshadow the heart sounds. The significant change is the muffling of the sounds, but particularly of the first heart sound. In addition the rhythm may have a peculiar foetal quality, and what is still more important is the great frequency of a gallop rhythm. This is present in the majority of cases and comes with the acceleration in heart rate. It practically always disappears if a satisfactory recovery takes place, and the heart slows down to normal. This gallop is not necessarily due to a delay in the conduction of beats from auricles to ventricles, although such disturbance in conduction does at times occur. Further examination of the heart may show a pericardial friction rub. A distinct pulsus alternans is another frequent finding. This may be made out by palpating the radial pulse, while taking the blood pressure, or occasionally on auscultation of the heart. In many cases some enlargement of the heart can be made out by percussion while in others the size will be found normal. One can see that of the above findings the evidence of hypertrophy and the presence of a systolic murmur are of little importance as they are insufficiently distinctive, whereas the extreme muffling of the heart sounds, the gallop rhythm, the pulsus alternans, and the pericardial friction rub are of considerable aid in diagnosis.

The abdomen not infrequently presents some significant features. The liver may become enlarged and tender. With this, or possibly independently of it, the upper abdomen may be quite rigid. There is occasionally a distinct icteric tint to the sclerae due to the acute hepatic engorgement. These features, together with the temperature and leucocytosis, and occasional vomiting, make one think that the condition is due to gall bladder disease. A further point in the examination is the presence of râles in the lungs. In almost all cases that have been studied râles were present at one or both bases of the lungs. In the milder cases they may be few in number, but in the more severe the râles can be generalized. The findings of localized râles, pain in the chest, cough, fever and leucocytosis, are so much like what are found in pneumonia that this diagnosis is wrongly made in some cases (cases 29 and 43).

At the beginning of the attack oedema of the legs is entirely absent and except for a few cases who develop evidence of generalized congestive heart failure, pitting oedema does not appear. The same is true of free fluid in the abdomen or chest. But those signs are to be watched for, as they alter both the prognosis and the treatment. Furthermore, there is a small number of instances in which pain is entirely lacking during an attack of acute coronary thrombosis (case 1). In such cases the entire complaint may be sudden dyspnea, either constant or in the form of attacks, with varying evidence of congestion of the lungs from a moderate number of râles at the bases to fulminating pulmonary oedema (cases 34, 46). With this there is apt to be a sense of extreme weakness or even unconsciousness.

It is in these atypical cases that the diagnosis will be difficult, and may depend on discovering one of the critical signs, such as a pericardial friction sound, an unusually low blood pressure, especially if there is reason to believe that hypertension previously existed, or changes in the electrocardiogram, which we will see later on may be considered significant. It is also important to try to uncover a previous history of angina pectoris, for if this has been present, a slight temperature and leucocytosis coming on after an increase in dyspnoea, or an attack of weakness, together with minor changes in the quality of the sounds, or rhythm of the heart, may lead to the proper diagnosis of coronary thrombosis.

Apart from the differences in pathological physiology that might explain why certain clinical features are lacking in some cases of coronary thrombosis, it must be borne in mind that even an acute attack, otherwise typical, may run its course without showing many of the customary changes that one expects. For example, one patient who was observed carefully from the onset never developed a heart rate faster than 62 although the temperature rose to 100.2° on the second day (case 123). The rectal temperature in this case six hours after the onset was 96.6°. In another case that was autopsied the blood pressure remained elevated in the vicinity of 160 mm. systolic until the day the patient died. A third had such mild symptoms that two days after the onset, not knowing what was going on, he attended to some of his practice as a physician while having transient auricular fibrillation and a fever of 100°F. (case 89). Furthermore, although severe pain in the chest is probably the most important feature of coronary thrombosis, it may be entirely absent. In such cases, very marked dyspnea, out of proportion to other evidences of circulatory insufficiency, is apt to be the dominating feature. In others, the clinical picture may be entirely one of acute pulmonary oedema.

b. Character and distribution of pain

The pain is variously described by different patients. To some it will be a terrible pressure or load "like a ton of bricks hitting the chest," or "a death clutch in the chest or throat." To others it will feel as if the chest were in a vise. Some cannot describe the pain and merely say "it was just an awful pain." The pain is generally most severe at the onset and in the course of several hours or days it gradually disappears. After this in some cases there is no pain whatever, while in others there remains a mild ache in the center of the chest. In other patients the pain is not constant but rather lasts a few hours, then lets up, only to return and continue interruptedly for a few days. With the development of pericarditis there need be no additional pain. Generally at this time the severe pain has already disappeared, or if there remains the dull ache, it is not particularly altered when the pericardial friction rub is heard. The pain radiates similarly to the pain in angina. Very frequently there is an uncomfortable ache in the arms, more often in the left arm. It often extends

directly through the chest to the back or up towards the neck and jaws, sometimes producing a clutching sensation in the throat. The most frequent site for the pain is between the two nipples but almost any portion of the chest from the epigastrium up may be involved.

The pain does not let up in a few minutes as it generally does with an anginal attack, but on the contrary lasts hours or even days. Relief is not obtained by the use of nitrites and with the very severe attacks even large does of morphine given subcutaneously may give only slight relief. The agony may be so extreme that the patient will be tearing his flesh in an attempt to get relief and crying for death to end his misery. In other instances, the pain is less severe and is associated with a feeling of a lump under the breast bone which if it could be expelled would end the attack. Often they are so agitated that they cannot lie down or be quiet, but prefer to pace the floor or thrash about. There are occasional cases in which the pain can hardly be described as severe. It may merely consist of a dull ache or an uncomfortable gnawing sensation in the chest that does not prevent the patient from continuing his work (case 89).

c. Atypical features of coronary thrombosis

In the foregoing account have been detailed the typical events that follow an acute attack of coronary thrombosis which occurs in a patient who generally has previously had angina pectoris. When coronary thrombosis develops in a patient who is already suffering from myocardial insufficiency, the picture that presents itself is not as striking, or at least may lack many of the features that characterize the typical acute attack. It is very likely that some of the characteristics of the acute form may be lacking when thrombosis of the coronary arteries takes place slowly, or when cardiac infarction develops as a result of gradual narrowing of the coronary arteries without any true thrombosis (cases 58 and 59). In general, it might be said that the acuteness of the symptoms and even the type of symptoms will depend in a great measure on the rapidity of the mechanical occlusion of the coronary arteries. Wearn (50, 51) in his most important work on the Thebesian vessels has shown how such channels may maintain a very extensive circulation through the heart and has thereby explained how hearts in which both coronary arteries were completely occluded

could function satisfactorily. No doubt in such instances the occlusion must have been gradual, thereby allowing proper adjustments to take place in the Thebesian system.

It is not at all uncommon to find at autopsy infarction of the heart, even with ventricular mural thrombi, without an actual occlusion of the coronary arteries, merely as a result of gradual narrowing of the vessels (cases 58 and 59). This was true especially in cases of so-called cardio-renal disease which showed evidence of progressive congestive heart failure. Such cases may have had at no time any acute episode to indicate either an attack of coronary thrombosis or cardiac infarction. The diagnosis in these cases is quite difficult but by no means impossible to make. One or more of the various findings pointing to cardiac infarction may be present even in the absence of any attack of pain and without any fall in the blood pressure. In one instance (case 6) angina pectoris was known to have been present for some years and then to have given way to dyspnea and signs of congestive failure. The blood pressure was 160 mm. systolic and 100 mm. diastolic throughout the illness, but the heart sounds were very distant and the electrocardiograms showed curves of extremely low amplitude. Autopsy showed coronary thrombosis, an old infarct of the left ventricle and a ventricular mural thrombus.

Occasionally there is very little to help in making a proper diagnosis (case 38). In this case there was hypertension, cardiac enlargement and circulatory insufficiency. The urine contained a large amount of albumin. The patient grew weaker, more dyspneic and died, the blood pressure remaining elevated throughout. Autopsy showed an infarct of the left ventricle with a mural thrombus. The coronary arteries, although thickened and somewhat narrowed, were patent. Here the ante-mortem diagnosis was impossible with the available data. There are instances where the development of a peripheral embolus first arrests attention to a left ventricular mural thrombus from which an embolus could be dislodged and thereby leads to a proper diagnosis (case 20). When a sudden hemiplegia occurs in a patient whose blood pressure is not remarkably elevated the diagnosis of cerebral hemorrhage is too often made. In some cases of this type the hemiplegia is due to an embolus and not to a hemorrhage and more careful search for other data pointing to coronary thrombosis should

be made. In case 20 the hemiplegia and the electrocardiograms enabled us to make a proper ante-mortem diagnosis.

d. Type simulating an acute surgical abdomen

Among patients suffering from acute coronary thrombosis, there is a small group, but none the less an important one, in which the diagnosis is particularly difficult. This refers to those patients who present the picture of an acute surgical abdomen. Some years ago (12) attention was called to this differential diagnosis after two such patients were observed. Since then other similar patients have been seen, and it is now felt that the proper differentiation in most instances can and should be made (cases 3, 26, 31, 44, 78, 127 and 145). Numerous publications have appeared emphasizing the apparent similarity of some of the symptoms in coronary thrombosis and perforated peptic ulcer or gall stones (52, 53, 54, 55, 56, 57).

It must be appreciated that although often a history quite typical of angina pectoris precedes the attack of coronary thrombosis occasionally no such warnings are present, and the very first indication of any serious trouble is the fulminating attack of pain. Moreover, this pain can be entirely confined to the upper abdomen or at least may be localized there during the first 12 hours or so. In this case vomiting is not at all rare, and in addition there can be jaundice, marked rigidity, and tenderness in the epigastrium and in the right upper quadrant. Furthermore, as we shall see, fever and leucocytosis frequently occur. When all the above findings are present in the same patient it may be difficult to avoid making the diagnosis of gall stone colic, ruptured gastro-duodenal ulcer, acute pancreatitis, acute appendicitis, or acute intestinal obstruction. All of the diagnoses mentioned above, which would demand an exploratory laparotomy, have been made on various patients that we have seen. In fact, the first time that this differential diagnosis presented itself (case 44) the patient was operated on immediately, and died on the operating table. It was only after the post-mortem examination was done that the true underlying cause was discovered, which proved to be a thrombosis of a coronary artery. It follows that a patient with coronary thrombosis may have excruciating pain in the abdomen, marked rigidity and tenderness in the upper abdomen, nausea, vomiting, slight jaundice, fever and leucocytosis,

and yet have no surgical lesion. Under such circumstances, every feature of the entire problem that may throw any light on the proper diagnosis will be important. It may be the marked muffling of the heart sounds, or the presence of a gallop rhythm, an alternating pulse, a pericardial friction sound, or a previous history of "indigestion" on effort that will direct the attention of the physician to the coronary arteries. In fact, minor considerations like the family history, or the general vigorous physique of the individual may be helpful in diagnosis.

Finally, when the possibility of coronary thrombosis is considered and electrocardiograms are obtainable, most valuable information might be had from such tracings. At times changes occur in the electrocardiograms that are so characteristic that no other data whatever would be necessary to make a positive diagnosis. In one such instance (case 26) the laboratory technician, who is not a physician, made the diagnosis of cardiac infarction from the electrocardiograms. This patient had mainly abdominal symptoms, and was having x-ray studies of the gall bladder and stomach. Despite the electrocardiogram the cardiac condition was disregarded, and the patient suddenly died. Post-mortem examination confirmed the diagnosis. The electrocardiographic changes referred to will be discussed below, suffice it for the present to say that they are important and helpful. It is also important to bear in mind that although these patients complain of pain in the upper abdomen, either at the same time or only a few hours later, in addition they generally complain of tightness of the chest of a type that is peculiar to coronary disease. A further point that is helpful in this difficult differential diagnosis is the fact that patients with coronary thrombosis are much more apt to have dyspnea than those with an acute surgical abdomen. It follows, therefore, that waiting a short time may make a doubtful diagnosis more certain and prevent an unnecessary surgical operation on a patient in whom such a procedure could prove dangerous.

e. Changes in the blood pressure

In 58 patients the blood pressure shortly before the attack of coronary thrombosis was either known to be high, or some of the readings during the attack indicated a hypertension. The average systolic

pressure of the group was 191 mm. and the diastolic was 110 mm. There were 38 males and 19 females, which is a proportion of two to one, with the males predominating, whereas the proportion is three and one-half to one in the entire series. This would indicate that among the smaller number of female cases of coronary thrombosis, there is a larger factor of hypertension than in the males.

There was no difference in the age incidence of this hypertension group as compared to the general average of the entire series, and the immediate prospect of recovery was not altered. In fact, it might be interpreted that a previous hypertension improves the prognosis slightly, for exactly one half of this group had an immediate recovery, while 46.7 per cent of the entire 145 cases recovered. Six patients were definitely known to have had a normal blood pressure before the attack of coronary thrombosis, and no doubt some of the others in whom no reliable data were available belonged to this group.

It is now quite well known that the blood pressure falls with coronary thrombosis. In many instances the exact level of the blood pressure was not known before the thrombosis, as they were first seen only after the attack had occurred. But in some the data was available. Furthermore, the average level of the blood pressure in angina pectoris is known to be 160.6 mm. systolic and 95.0 diastolic (19), and has been found to vary from normal readings to marked hypertension. It is obvious, therefore, that the fall in the blood pressure that commonly is seen is apt to be more marked if a previous hypertension existed than if the pressure was normal. For example, one patient (case 11) was known to have had, a short while before the thrombosis, a systolic blood pressure of 200 and diastolic 110, and when first seen two hours after the attack the readings were systolic 160 and diastolic 90; a few hours later the readings were 120 systolic and 80 diastolic. The following day the systolic pressure had fallen to 110. This illustrates a marked gradual fall occurring in several hours. Another patient (case 40) was in the hospital at the time the attack of thrombosis occurred, and the previous readings of the blood pressure were known. The general average was systolic 150 to 160, and diastolic 95. The day following the thrombosis, and for one month thereafter, the systolic pressure ranged around 95 to 105, and the diastolic 65 to 75. Here, naturally, the fall was less because the original level was lower. It will

be noted that the fall in pressure affects both the systolic and the diastolic readings. In a third instance (case 42) the diastolic pressure which was 130 before the attack fell to 70 three days after the attack. Both of these latter two patients recovered. Even when the pressure is normal before the attack, an appreciable fall may take place. One patient was observed in whom the readings were between 125 and 130 systolic, and 85 to 90 diastolic. After the attack the pressure fell to as low as 92 systolic and 72 diastolic.

Occasionally the blood pressure remains high. This was well illustrated in case 7. Two weeks before admission this patient had a typical attack of pain in the chest. She died ten days after coming into the hospital. During her stay various blood pressure readings were made, and they ranged around 180 to 190 systolic and 85 to 100 diastolic. Post-mortem examination showed typical cardiac infarction with a mural thrombus in the left ventricle. Several other such instances were found. It is quite possible in such cases that the blood pressure was much higher before the attack.

In many cases that recovered, in which a fall of blood pressure occurred, the pressure remained at a lower level thereafter even while the patient returned to full activities. There are, however, other instances in which shortly after the first few days the blood pressure rose again as the patient improved. This was true of cases 28, 55, 81, 111 and 135, in which the systolic fall averaged 82 mm. and the diastolic 34 mm. and with recovery the rise was 53 mm. in the systolic and 27 mm. in the diastolic reading. In other words, the recovery in the blood pressure, although considerable, was not complete.

The fall in blood pressure is generally quite rapid. In the instances where death occurred in minutes or hours, pressure readings frequently were not obtained, but it is obvious in these cases that the pressure probably was extremely low, as the patients often were pulseless. When death does not occur during the early days the fall in pressure may either take place immediately, so that the first reading is the lowest, or it may gradually fall during the first 12 to 24 hours, as occurred in case 11. During the process of recovery the blood pressure is apt to rise slightly from the lowest figure, but in most cases does not return to the high level that existed before the attack. It has been our general impression that the patients who have done best were those who

showed a marked fall with only a slight subsequent increase in the blood pressure (28). It is striking that in these cases where recovery was satisfactory, the blood pressure remained low even when they returned to work, and has never risen over a period of some years of observations. A further interesting feature is that with these lower pressures the patients who suffered from angina pectoris before the attack of thrombosis, thereafter were practically or entirely free from anginal attacks.

f. The development of fever and leucocytosis

In the great majority of acute cases of coronary thrombosis, there quickly develops a fever and leucocytosis. This has been noted as soon as a few hours after the onset. It has often been our experience that fever was considered absent as the result of taking a mouth temperature, but on determining the rectal temperature an appreciable fever was found (case 95). During the early hours of the attack, the patient may be in collapse, feel cold, show a clammy moist skin and be quite dyspneic. For one reason or another the mouth temperature may read 97° or 98° when the rectal temperature would show a fever 100° to 102°. This is a most important point that is frequently overlooked, and occasionally is rather critical in deciding whether an attack of chest pain is due to angina pectoris or to coronary thrombosis.

The fever may last from one to several days, or as occasionally happens, it may continue for one to two weeks (case 16). It occasionally rises to 101°, 102° or more, but generally is about 100°. The disappearance of the fever is gradual, usually without any recurrences when the patient's progress is favorable. There are rare instances when fever is absent throughout the illness, even when the rectal temperature is taken (cases 68 and 123). The extent of fever and leucocytosis probably depends on the amount of infarcted cardiac tissue involved. It is a clinical experience that whenever infarcts of parenchymatous organs occur, even in the absence of infection, a fever and leucocytosis may develop. This is frequently seen when cardiac patients dislodge emboli from sterile mural thrombi in the right or left auricle, and develop pulmonary, cerebral, splenic or renal infarcts. It may be stated that infarcted tissue anywhere in the body probably liberates toxic products that produce leucocytosis and fever.

The leucocyte count is apt to run hand in hand with the fever. This also becomes elevated early and may remain above normal for several days. Occasionally the leucocytosis lasts 10 to 14 days (case 35). Rarely there is no leucocytosis even in the presence of a slight fever (cases 36, 37 and 139). It has been stated by Libman and Saks (58) that a leucocytosis may develop as early as one and one quarter hours after the onset of symptoms. The increase in the white cells of the blood is apt to be slight or moderate. A common count is about 12,000 to 15,000 but may reach 25,000 or more. With this there is a distinct increase in the polymorphonuclear ratio, which rises to 80 per cent and sometimes to even 90 per cent (case 57). The leucocytosis lasts as long as the fever does, and at times lags a day or so longer. Some years ago (12) the significance of this leucocytosis and fever was noted, particularly in cases with abdominal pain when one could easily mistake the condition with an acute surgical emergency.

The presence of a leucocytosis is one of the most constant findings in coronary thrombosis. Out of 74 cases in which data were obtainable there were only four who had white blood cell counts within normal limits, i.e., under 10,000, during the first week following the onset of the attack. To be sure, there were some who when first seen after seven or 10 days had no leucocytosis. One patient (case 140) had a count of 7,400 six days after the onset, another (case 65) had counts of 7,700 to 6,600 one and eight days after, a third had a count of 7,900 one day after, and a fourth had 8,600 four days after the attack. It may be true that even some of these would have shown a distinct leucocytosis if more frequent counts had been made.

g. The occurrence of pericarditis

An acute pericarditis not infrequently develops following an attack of coronary thrombosis. The only clinical evidence of this is the presence of a pericardial friction rub. When present this is first heard over the lower precordium in the vicinity of the left nipple and towards the sternum. It does not occur in the majority of cases; in fact, only about 13.8 per cent show this sign. The mechanism of this type of pericarditis is rather clear and simple. After the coronary vessel is either partially or completely occluded, the heart muscle that was supplied by that artery becomes infarcted. If the process of infarc-

tion is so extensive or so situated that it extends sufficiently to the surface to involve the visceral pericardium, a local inflammation and irritation develops at the injured site. When the location of the affected part of the heart is anterior, a pericardial friction rub may be heard. If the process involves the posterior or diaphragmatic portion of the heart or the interventricular septum, no friction rub will be heard, and if it does not extend to the outside portions of the heart wall there will be no pericarditis. It follows from the above that the pericardial rub is a variable sign but extremely helpful from the point of view of diagnosis.

This pericardial friction rub is a to and fro murmur and differs only slightly from the similar sounds heard in rheumatic pericarditis. It is not apt to be as loud nor is it apt to last as long. Whereas in the latter condition it first appears and is generally best heard near the third left sternal border, here it is best heard more frequently further down and out near the left nipple. Although the friction rub when present is first heard one to several days after the onset of the attack, it may become audible in a few hours (case 145). The signs of compression of the left lower lobe of the lung that are frequently made out below the angle of the left scapula in cases of rheumatic pericarditis are never present in this condition. Furthermore, we have had only one instance of pericardial effusion in this series (cases 64), and the development of the pericarditis has not produced additional symptoms like pain or elevation of the temperature or pulse. The presence of a pericardial friction in general indicates a fairly extensive area of cardiac infarction, but by no means signifies a hopeless prognosis, as there were seven recoveries and 13 fatalities of 20 cases in which it occurred.

h. Changes in the urine

Coronary thrombosis generally occurs in patients who previously showed very little evidence of renal insufficiency. In most instances where the patients were previously examined, the urinary findings were practically normal and the kidney function tests were within normal limits. Occasionally the urine showed a slightest possible trace of albumin, and an occasional hyaline cast similar to what one commonly discovers in patients with vascular hypertension or arteriosclerosis without nephritis. Frequently, however, a true comparatively mild

diabetes had existed for some years before the development of coronary thrombosis. In such instances sugar may be present during the acute attack in greater amount than what was found previously. On the other hand, there were instances where no diabetes was present and yet during the attack a slight or moderate glycosuria was found. In several cases the finding of about two per cent sugar in the urine and an accompanying acidosis of a moderate degree were sufficient to obscure the diagnosis and brought up the possibility of a diabetic acidosis or pancreatitis. In some cases there apparently was a co-existing true diabetic acidosis and coronary thrombosis (cases 49, 53 and 68). It is important to appreciate that glycosuria is a common occurrence during the acute stages of coronary thrombosis, that it may be transitory, and that it need not indicate any important diabetic state. It often proves to be a concomitant of the shock and terrific pain that exists with this condition.

A further feature of the urinary findings is the presence of albumin, casts and cells. During the first few days while the acute process is going on, and there is fever and pain, the urine may resemble what one finds during an active nephritis. These changes are also transitory and when recovery occurs the urine returns to a normal state. Very often the urine becomes quite scanty and there may be a practical suppression of urine during the first day or so. This probably results from the state of shock and the markedly diminished arterial blood pressure. In an occasional case quite a different condition may occur. There are some instances (case 39) where in the wake of the coronary thrombosis, hematuria develops. This takes place when emboli are dislodged from the mural thrombus that commonly forms within the cavity of the left ventricle adherent to that portion of the heart that becomes infarcted. Such emboli occasionally lodge in the kidneys and here produce secondary renal infarcts. In this manner gross or microscopic hematuria may result from which recovery can take place.

i. Disturbances in the rhythm and mechanism of the heart beat

It is a striking fact that coronary thrombosis almost invariably occurs in patients previously having essentially a normal heart rhythm. A corollary of this observation is that it almost never develops in a patient who previously had persistent auricular fibrillation. Of the

large number of elderly individuals who have chronic myocarditis and auricular fibrillation, with various evidences of heart disease, we have only seen one who developed coronary thrombosis, and in this case the diagnosis of the previous arhythmia was not absolutely certain as no electrocardiograms were taken at the time. There seems to be the same incompatibility between these two conditions as has been found to exist between auricular fibrillation and angina pectoris (19). The former has an apparent protective influence over the latter, and one may with safety predict that a patient with persistent auricular fibrillation is most unlikely ever to develop coronary thrombosis.

Although the rhythm of the heart is normal to begin with, and remains so essentially during attacks of angina pectoris, it is quite otherwise when coronary thrombosis develops. With the latter almost any form of cardiac irregularity may be found. The frequency with which they will be observed will depend entirely on the care and frequency with which the patient is studied, for many of the disturbances are very transient, lasting only hours or might not be detected except with the more complicated methods of graphic representation of the heart beat, like the electrocardiograph. It is important to contrast the rarity of disturbances of the heart rhythm during anginal attacks with the frequency of them in coronary thrombosis.

Some of the irregularities are less striking than others. Premature beats are frequently observed during the acute stages of the attack, but inasmuch as they occur commonly in normal individuals, and with almost any type of heart disease, they are not of any particular significance. They are generally ventricular in origin, but may be auricular. There were 35 cases in which extrasystoles occurred, and of these 19 were fatal and 16 recovered. This would indicate that they have no prognostic importance. More important than this is the sudden development of heart block. Any degree of auricular-ventricular conduction disturbance may be found during the early days following an attack of coronary thrombosis. Simple delay in the conduction time of impulses, resulting in a regular heart rhythm without blocking of beats (fig. 45, case 32, and fig. 59, case 139) or actual partial heart block of varying degrees, is not uncommon. Sudden halving of the heart rate is a not infrequent event (fig. 29, case 9). This results from the blocking of every other impulse from the auricles. At other

times, one finds merely an occasional dropped beat on auscultation over the precordium (fig. 42, case 35). There were nine cases in which partial heart block was noted, and of these five died and four recovered. Here again the disturbance did not affect the general prognosis. Finally, complete heart block occurs rather infrequently. The first case in which the ante-mortem diagnosis of coronary thrombosis was made by one of us (12) showed sudden complete heart block with a heart rate of 28, and it was this particular finding that led to the proper diagnosis (fig. 71, case 3). This has been seen one other time, and in both of these cases the patient died. We have heard of instances, however, in which recovery took place despite the development of complete heart block (59). It must be understood that although attacks of syncope may be explained in some instances as a result of heart block and the accompanying temporary standstill of the ventricles, other patients may become unconscious without heart block, mainly as a result of the extreme state of collapse and the insufficient circulation. Complete heart block may need special treatment, such as adrenalin as an emergency measure, and, therefore, one must be alert to note its development.

There remain two other disturbances in the mechanism to be considered, i.e., auricular fibrillation and ventricular tachycardia. Paroxysms of auricular fibrillation are quite common during the first few days of the attack (figs. 40, 74 and 80). They occur with much greater frequency than is generally noted because such attacks are apt to last but a short time, and are often not observed. We noted this disturbance in 34 of our patients, including one case of auricular flutter. In these cases the heart rhythm suddenly became rapid and grossly irregular, and there was present a distinct pulse deficit. The rate of the heart generally was about 140 or 150, and the patient was either

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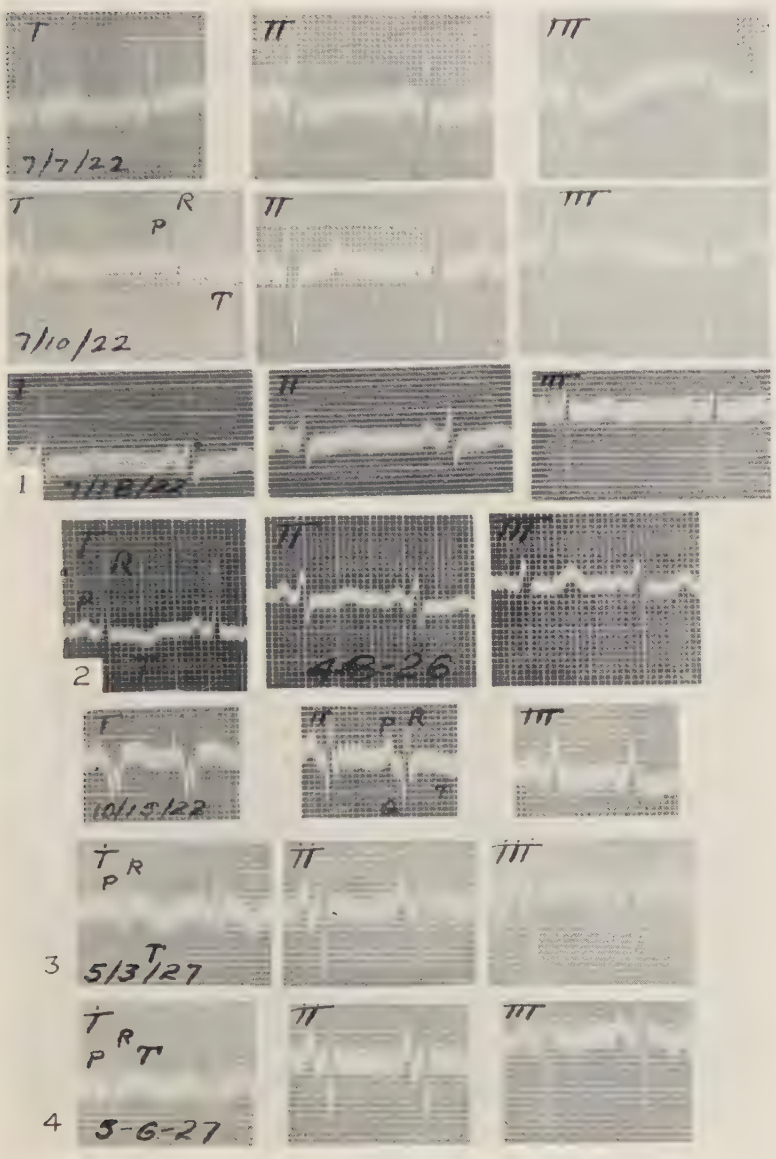
FIG. 1. Case 15. Attack July 6, 1922. Note minor changes in the form of the T wave.

FIG. 2. Case 72. Attack February 4, 1926. Note absence of any striking changes 2 months after attack.

FIG. 3. Case 17. Attack September 30, 1922. The Q R S waves have a bizarre form, are coarsely notched, and are of low amplitude. Patient recovered and died about 4 years later.

FIG. 4. Case 140. Attack May 2, 1927. Note the peculiar inverted dipped T wave in lead 1 one day after the attack, which disappeared in three days. Patient recovered.



FIGS. 1-4

unaware of the new change that had taken place, or, more rarely, he developed severe symptoms of marked dyspnea and circulatory insufficiency. If the latter occurs, proper measures to support the circulation, such as digitalis and caffein, might be necessary. In most instances the attack of auricular fibrillation lasted one to several hours and then disappeared even if no special treatment was administered.

The development of paroxysmal auricular fibrillation in coronary thrombosis did not alter the prognosis of the case, for of the 34 instances, in 16 recovery took place and 18 were fatal. One may further add that some of the most satisfactory recoveries occurred in this group. Occasionally, however, one such attack initiates the persistent form of auricular fibrillation (figs. 9 and 49), and the patient from then on requires proper digitalization to keep the ventricular rate slow as any patient would who has this disturbance in rhythm. It follows from the foregoing that, although coronary thrombosis is rare in patients who previously had persistent auricular fibrillation, it is common for this arhythmia to develop, generally in a transient form, after such an attack.

A much rarer but in some ways a more important disturbance is the development of paroxysmal ventricular tachycardia (figs. 37 and 61). The association of this arhythmia with coronary disease was emphasized by Hermann and Robinson (60, 61). This condition is almost always associated with grave coronary disease in contra-distinction to the other arhythmias that have been discussed, which, although occurring in coronary thrombosis, are often met with in other conditions. In paroxysmal ventricular tachycardia the heart suddenly becomes rapid with a rate of about 150 to 200 and remains essentially regular. It has generally been considered that it is impossible to

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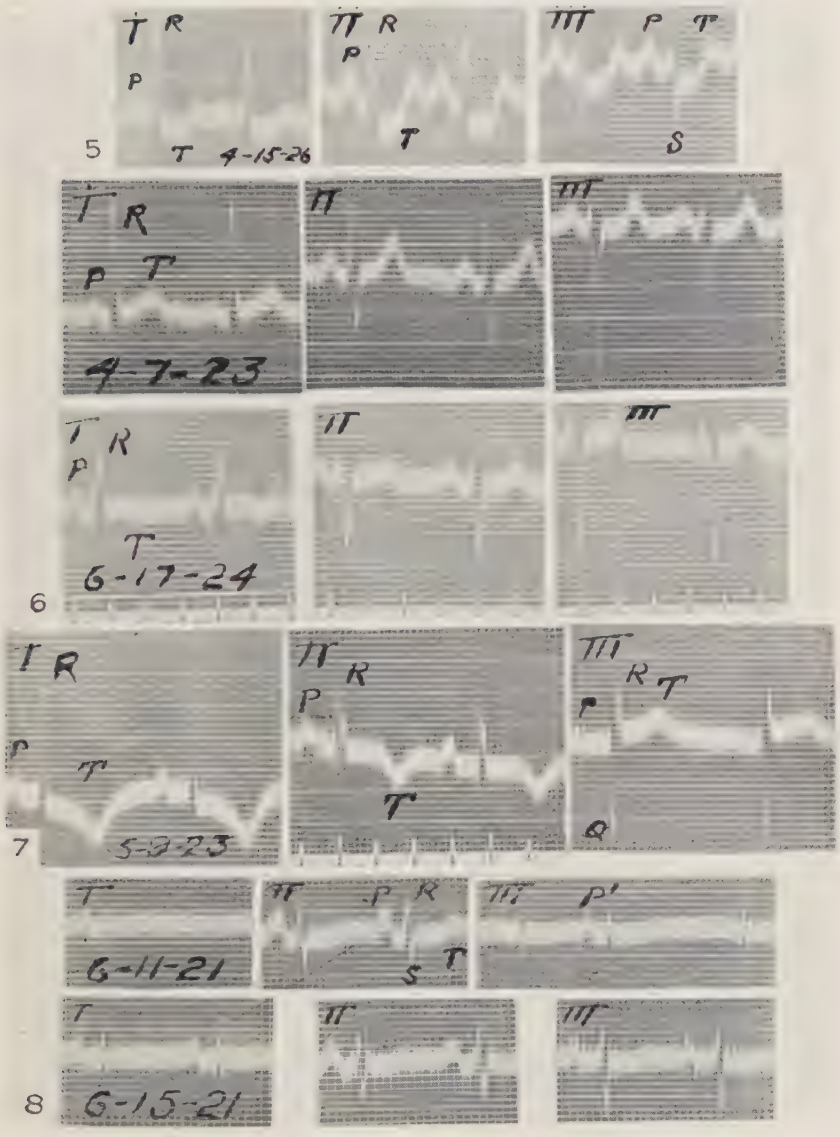
Fig. 5. Case 62. Attack April 8, 1926. Note low take off of the T wave in leads 2 and 3. Patient died the same day.

Fig. 6. Case 39. Attack April 8, 1923. Curves one day before the attack were not remarkable, and those later showed slight slurring of the Q R S complexes, and a flattening of T. Patient recovered well and died suddenly about three years later.

Fig. 7. Case 20. Attack probably May 8, 1923. T 1 is sharply inverted, and the upstroke of T 3 begins slightly above the base line. Patient died May 22, 1923. Autopsy showed infarct of left ventricle.

Fig. 8. Case 11. Attack June 10, 1921. Died suddenly June 22, 1921. Note the low amplitude of the ventricular complexes.



FIGS. 5–8

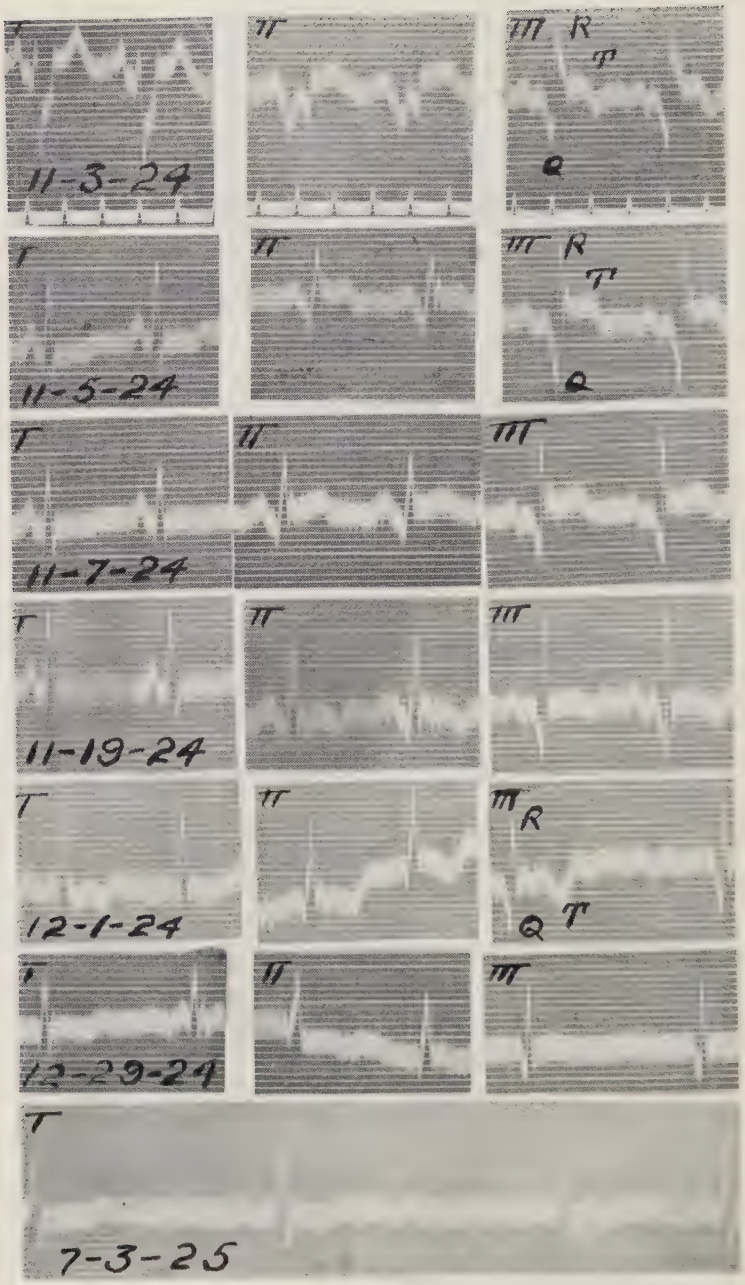


FIG. 9. Case 55. Attack October 25, 1924. Note high take off of T 2 and T 3 which gradually becomes inverted and then flat. There are also prominent Q 3 waves. The first tracings are particularly bizarre and indicate a probable defect in conduction of left branch of bundle of His. The latter curves show permanent auricular fibrillation. Patient died February 15, 1926.

recognize this condition at the bed side and that it requires electrocardiograms for its differentiation from other heart disturbances with rapid rates. Very recently several features in this connection have been investigated that have enabled us to make a proper bed side diagnosis in four instances and promise to be valuable aids in the future where confirmatory evidences by electrocardiogram are not available. In auricular fibrillation the rhythm is absolutely irregular while here it is essentially regular. It is important to bear in mind that slight irregularities in the rhythm may be heard on careful auscultation over the precordium. This point has been emphasized as an aid in distinguishing ventricular from auricular tachycardia (62). The rhythm, although in the main regular even for fairly long periods of time, will every now and then be interrupted by a slight pause which can be readily detected by the ear. A further distinguishing feature between this type of tachycardia and paroxysmal auricular tachycardia, or auricular flutter, is that it is absolutely uninfluenced by vagal pressure. The latter two conditions on the other hand may be affected by pressure over the carotid arteries; the one frequently being entirely arrested and the other temporarily slowed by such a procedure. A final distinguishing feature is that during ventricular tachycardia one may not only hear occasional slight irregularities in the length of the heart beats, but the intensity of the first sound of the heart at the apex may vary. A curious sudden clicking, reduplication or snapping sound may be heard with various cycles (63). This, one may suppose, results from the simultaneous contraction of the auricles and ventricles that takes place at times or at least from the variation in relationship between ventricular and auricular systole that occurs in this condition. The situation is not unlike complete heart block where a similar variation in quality of the first heart sound takes place.

This discussion has been taken up in some detail because on occasions the proper clinical diagnosis of ventricular tachycardia and the subsequent appropriate treatment of it may make the difference between the life and death of the patient, as was illustrated by case 134 (64). When the patient is in a hospital where electrocardiograms can be taken, the diagnosis is not difficult, but inasmuch as most patients suffering from coronary thrombosis are in their homes, the bed side aids in diagnosis are of primary importance. Furthermore, this condition,

although in some cases transient and only lasting several hours, can persist for days and produce increasing symptoms of circulatory insufficiency with death from exhaustion. Under such circumstances, death may properly be ascribed to the uncontrolled rapidity of the ventricles. Below, when the question of treatment will be discussed, the proper course to follow in order that this disturbance in the mechanism of the heart may be checked will be gone into in detail because, although uncommon, it is most serious and much can be done for it.

A final disturbance that is most frequently met with during the active stage of coronary thrombosis is the gallop rhythm. If careful auscultation is carried out during the early days following an attack of coronary thrombosis, it is not unlikely that in most patients a true gallop rhythm will be heard. Here there is no change in the rhythmicity of the heart or in the conduction of impulses, but there is a definite change in the quality of the heart sounds. It is generally best heard in the vicinity of the left nipple and unlike a splitting of the first or second heart sounds, it is a true canter or gallop. The heart rate at this time is generally elevated to about 100 to 120, and the exact timing of the extra sound in the heart cycle is not simple, but one gets the impression that it is of the presystolic type. The detection of a gallop rhythm may seem to be of minor importance because it is present in other conditions than coronary thrombosis, but because in some cases the diagnosis is quite obscure and difficult, any clinical feature may under those

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FIG. 10. Case 1. Attack May 3, 1915. Note very low amplitude of complexes and rounded and dipped T 2 and T 3. Patient died May 9, 1915. Autopsy showed ruptured left ventricle.

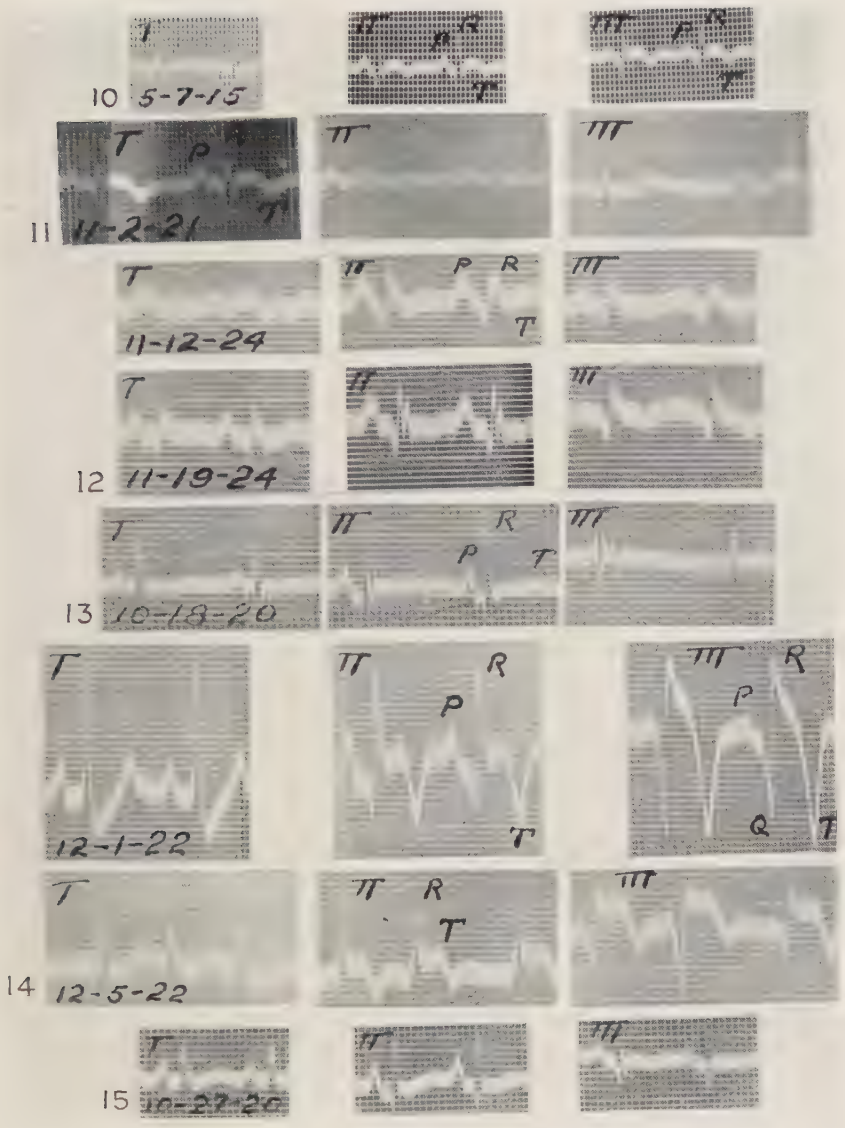
FIG. 11. Case 132. Attack September 3, 1921. Note low amplitude of ventricular complexes and dipping of T 1. Patient recovered. Ultimate outcome not known.

FIG. 12. Case 33. Attack November 11, 1924. Note low amplitude of Q R S waves, and coarse notching. Patient died November 20, 1924.

FIG. 13. Case 7. Attack October 4, 1920. Tracings are not remarkable. Died October 28, 1920. Autopsy showed infarct of left ventricle.

FIG. 14. Case 18. Attack November 27, 1922. (In first tracings there was over shooting.) Note high take off of T 2 and T 3 and development of auricular fibrillation in the second tracings. Died December 8, 1922. Autopsy showed infarct of left ventricle.

FIG. 15. Case 8. Attack October 21, 1920. The Q R S waves are rather small. Died October 27, 1920. Autopsy showed rupture of left ventricle.


10
5-7-15
11
11-2-21
11-12-24
12
11-19-24
13
10-18-20
12-1-22
14
12-5-22
15
10-27-20

FIGS. 10–15

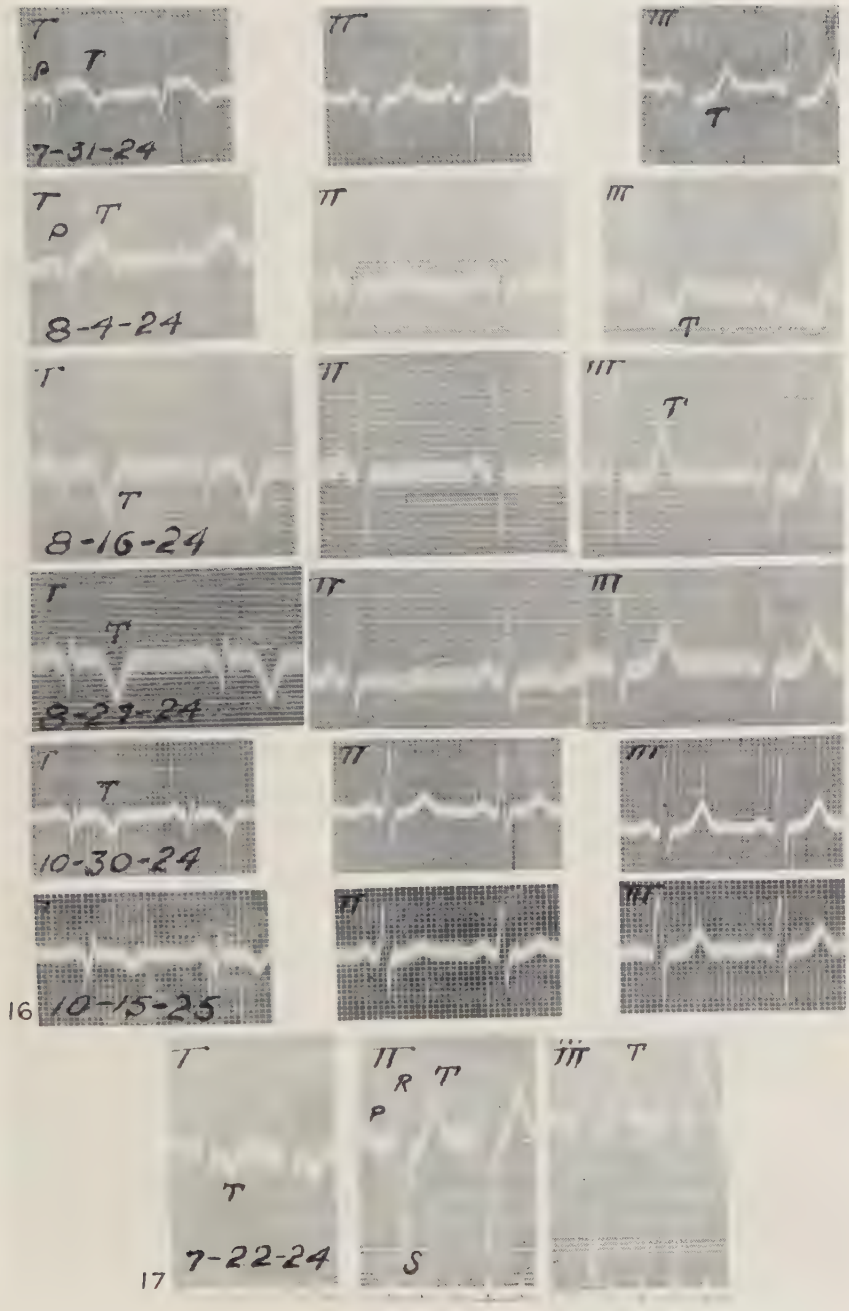
circumstances be of sufficient weight to swing the balance in the proper direction.

j. Modes of death in the fatal cases

There is great variability in the time that death occurs and in the mechanism of the fatal events in coronary thrombosis. Familiarity with these facts is important as it helps the physician in the treatment of the problem and enables him at times to anticipate certain events and possibly prevent catastrophies. This subject has recently been discussed at some length by Fulton (65). From the moment that the attack begins death may occur at any time until a period of several weeks has elapsed, although the cause of death is quite different at different times. The group of patients in whom death occurs instantly is of comparative less clinical interest than when the immediate result is not fatal, because in the former the physician is called only to pronounce the patient dead. There are many instances in which ambulatory anginal patients without any warning, either while at rest at home or at their work suddenly cry out and fall dead instantly. The coroner has long since examined such patients and found nothing or on careful examination a thrombosis of the coronary arteries might be discovered. To be sure there are occasional instances where the coronary arteries are found sclerosed or narrowed but not occluded, and yet the shock proved to be fatal. Sudden fibrillation of the ventricles can be offered as a satisfactory explanation of such a sudden death were sufficient pathological evidence is not found at autopsy. It can also explain the sudden death that occurs some days after the onset of the attack when the patient was apparently doing fairly well, in which rupture of the heart did not occur and no embolic phenomena had taken place. In fact ventricular fibrillation explains quite well such unexpected fatalities, but the hypothesis does not readily lend itself to proof as rarely is an electrocardiogram taken at that time to confirm this theory.

FIG. 16. Case 30. Attack July 20, 1924. Note high take off of T 1 and corresponding low take off of T 3. The T wave then goes through striking changes developing the characteristic sharp V shaped form in lead 1. This patient has remained very well for over $3\frac{1}{2}$ years.

FIG. 17. Case 29. Attack July 20, 1924. Note rounded dipped T 1 and prominent upright T 3. Died July 24, 1924. Autopsy showed thrombosis of left coronary artery.



Figs. 16–17

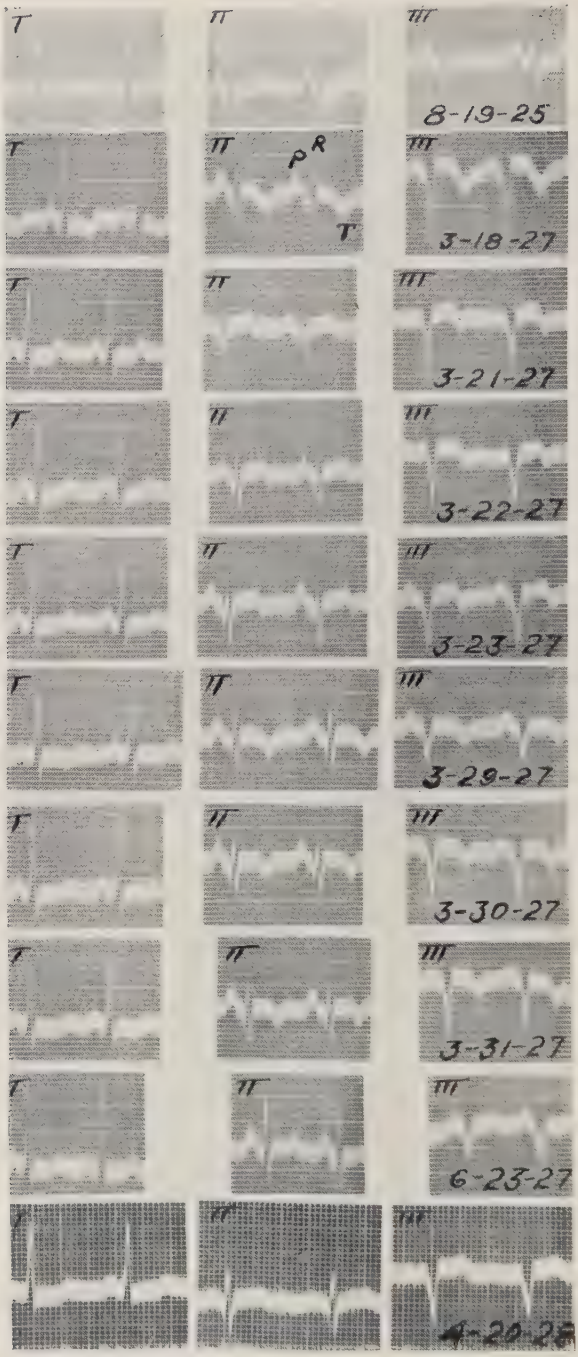


FIG. 18. Case 143. Attack March 16, 1927. First tracings taken a year and one-half before attack. Note slight but significant changes in the form of T wave in all leads. Patient recovered and has done well.

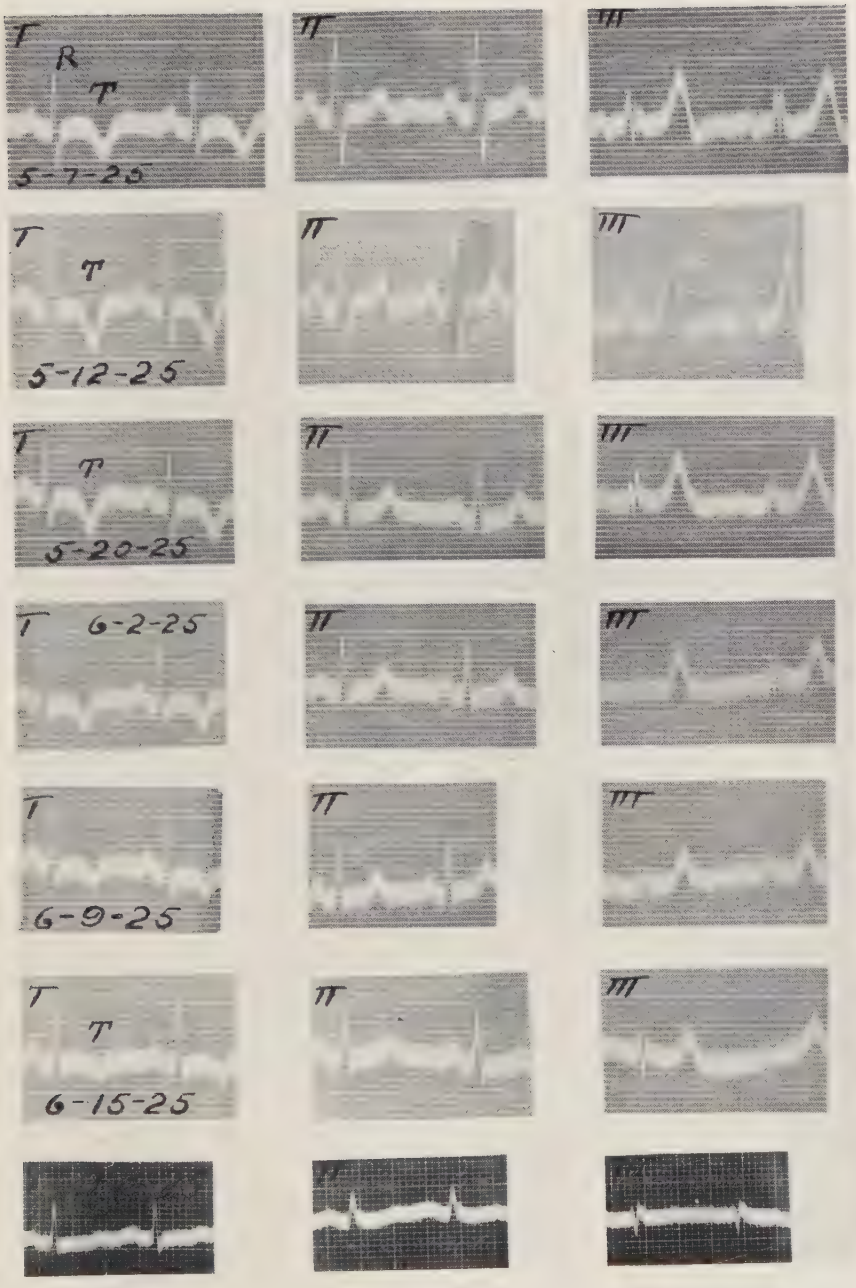


Fig. 19. Case 54. Attack April 27, 1924. Note the rounded and dipped form of T 1 and prominent upright T 3. Patient recovered and has done quite well for over 2½ years.

When the patient survives long enough for a physician to attend him, general failure of the circulation may result within one to several hours. Here the shock to the circulation is sufficient to depress the blood pressure to very low levels, such as 60 or 80 mm., or the pulse may be entirely imperceptible. The patient then presents the picture of profound shock and may be actually unconscious. This can occur even when the heart is contracting regularly. Another type of unconsciousness is the one that results occasionally with actual temporary standstill of the heart and complete heart block (case 114). Death may occur much in the same way as it does in the ordinary case of Adams-Stokes disease from a prolonged heart block. Under such conditions the conduction apparatus is involved, and death occurs even when one might have expected that the heart would have survived the attack if some sort of ventricular contractions could have been induced. In such instances it would seem that the administration of adrenalin might prove helpful to tide the patient over for a short period of time, while a new adjustment is being established. When block does not occur, and the patient presents the picture of extreme shock and low blood pressure, death may follow merely from the results of an enfeebled and insufficient circulation. Although we have seen many such instances in which the heart remains regular though rapid throughout, the fact that occasionally ventricular tachycardia develops makes it not unlikely that sudden death can be explained on the theory that there develops a ventricular fibrillation which is a degree of ventricular irritability slightly higher than that which obtains in ventricular tachycardia, and which produces an

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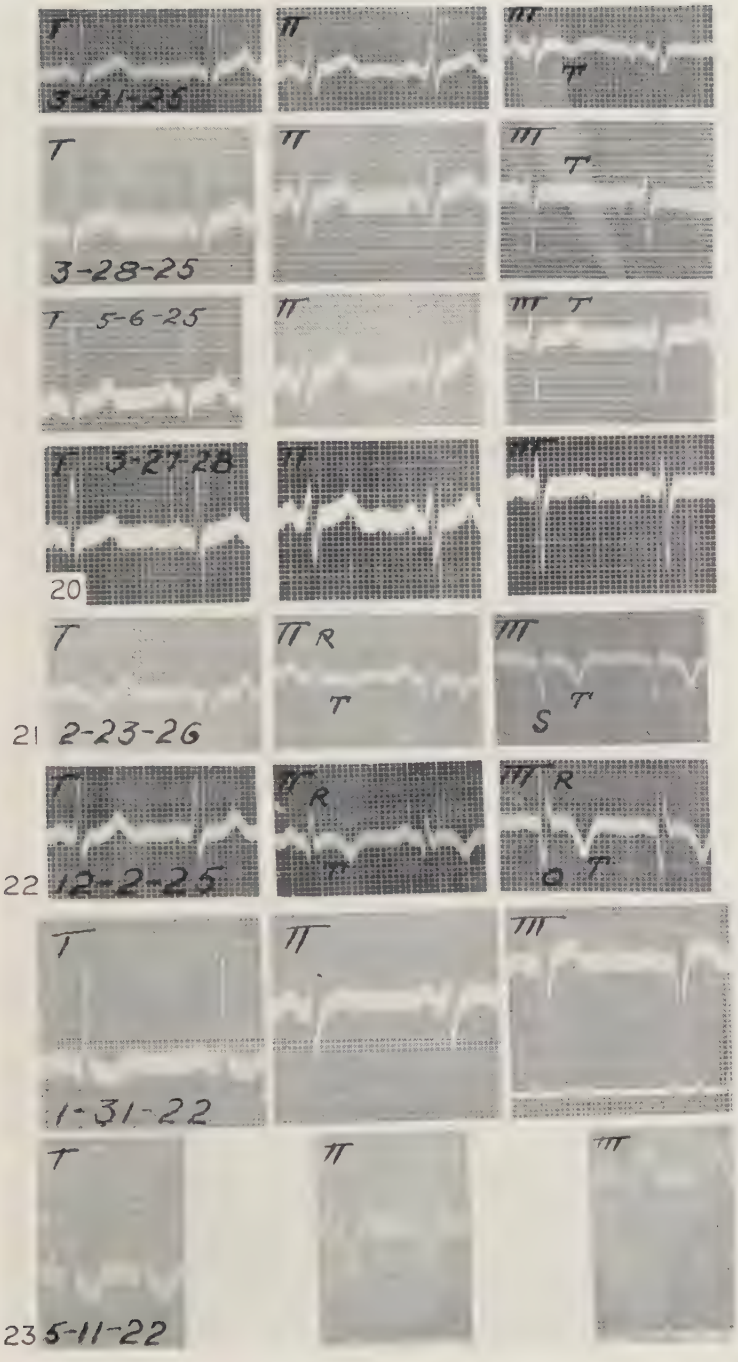
Fig. 20. Case 51. Attack March 13, 1925. Note rounded slightly dipped T 3 in first tracings. The following curves are not remarkable and illustrate how easy it is to miss significant changes because of their transient character. Has recovered and done well for over 3 years.

Fig. 21. Case 80. Attack February 18, 1926. Note slight curving of T 2 and sharp inversion of T 3. Patient has recovered and done well for 2 years.

Fig. 22. Case 82. Attack October 1, 1925. Form of T 2 and T 3 is fairly characteristic. These curves illustrate diagnostic importance of previous attack of coronary thrombosis. Patient had immediate recovery but ultimate outcome unknown.

Fig. 23. Case 14. May 11, 1922. Date of attack not determined. Tracings not remarkable. Died May 14, 1922. Autopsy showed an old infarct of left ventricle and a mural thrombus.


I
II
III
T
3-21-25
3-28-25
5-6-25
3-27-28
20
R
S
21
2-23-26
22
12-2-25
Q
1-31-22
23
5-11-22

FIGS. 20–23

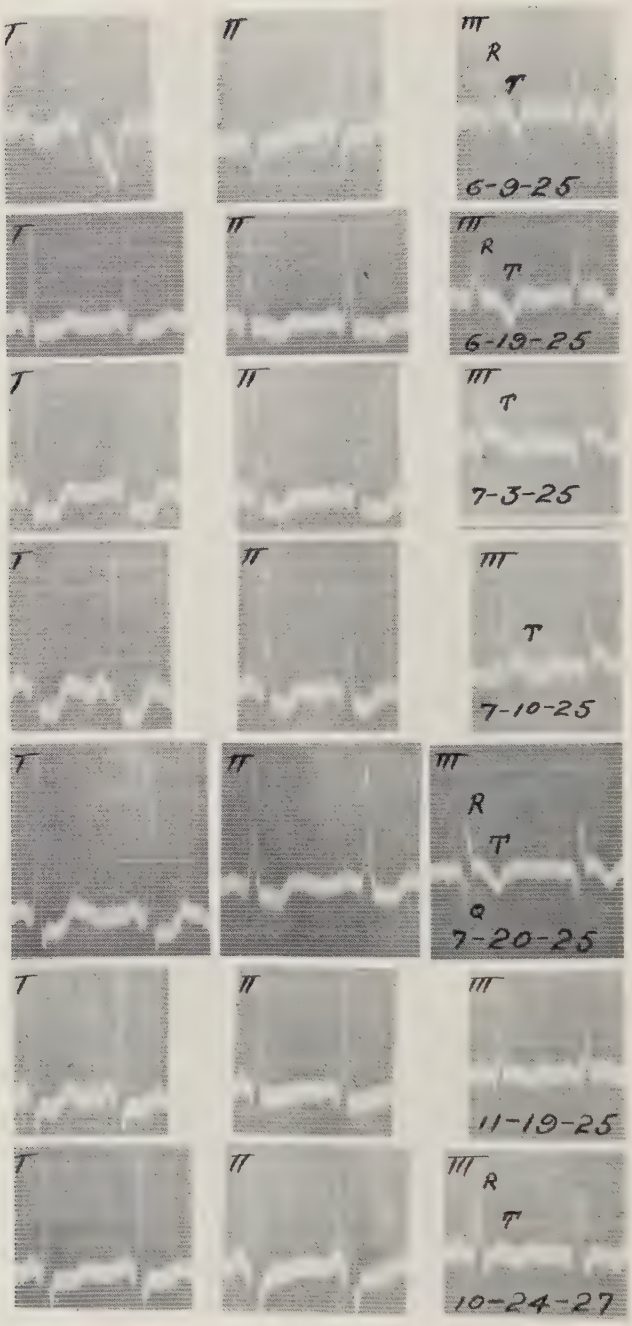


FIG. 24. Case 56. Attack May 9, 1925. First tracing shows one premature ventricular beat. Note changes in form of T wave especially in lead 3. It is interesting that typical high take off occurred almost 2 months after attack (July 3, 1925). A Q wave developed in lead 3 and then disappeared. Patient recovered but continues to have angina.

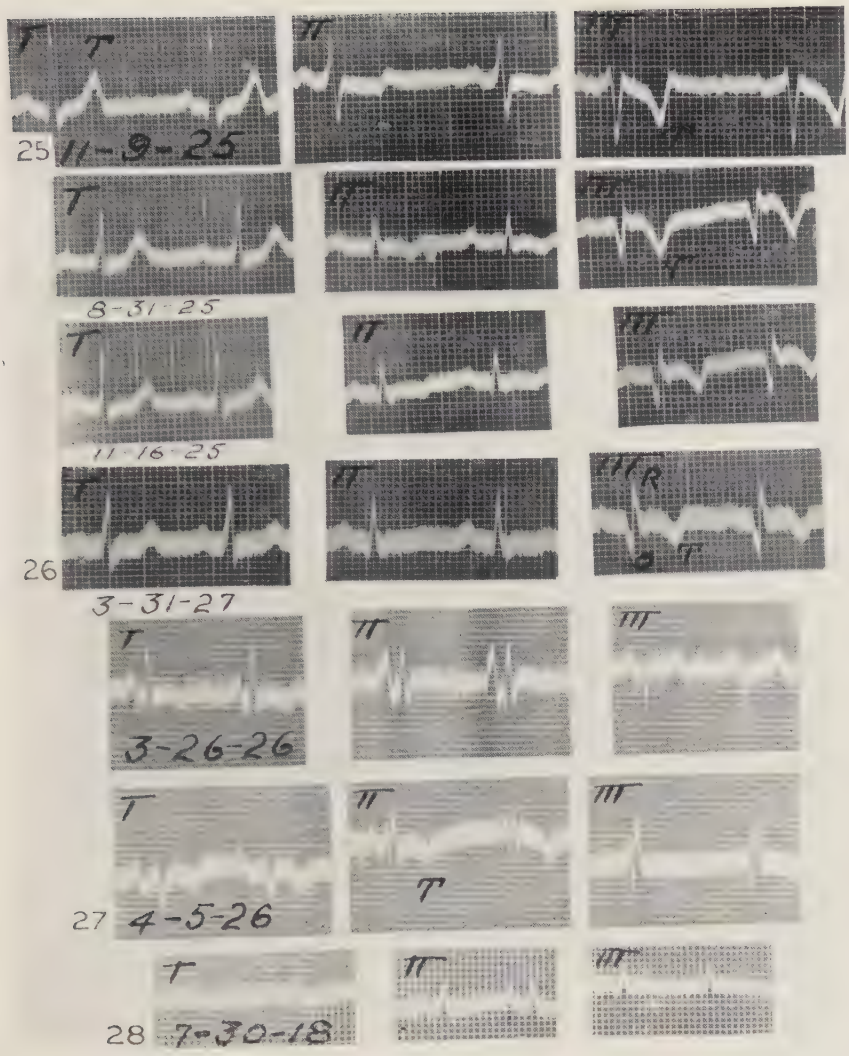


FIG. 25. Case 83. Attack November 2, 1925. Note sharp inversion of T 3 with corresponding prominent upright T 1. Patient recovered but since has had frequent angina attacks.

FIG. 26. Case 86. Attack August 17, 1925. Note sharp inversion of T 3 and the presence of a definite Q 3. Patient has done well for past $2\frac{1}{2}$ years.

FIG. 27. Case 63. Probable date of attack March 10, 1926. Note that the characteristic changes in T wave appeared late. Q R S waves are somewhat small. Died April 5, 1926. Autopsy showed left coronary thrombosis.

FIG. 28. Case 6. Probable date of attack August 30, 1918. Note extremely low amplitude of ventricular complexes (these curves were accurately standardized). Died 1918. Autopsy showed thrombosis of left coronary artery.

abrupt cessation of the heart beat. How often this does occur it is impossible to state, as it would be only a rare fortuitous experience if one actually obtained electrocardiograms at the moment of the final exitus.

When the patient survives the first day or two, marked and rapid improvement may then take place so that he can enjoy a sense of complete well being and freedom from symptoms. Despite this, death may occur unexpectedly between the fifth and tenth day from an actual rupture of the heart through the infarcted area. Case 1 illustrates this very strikingly. One of us was attending this patient and had just examined him and in answer to a question he replied that he was feeling splendidly. He was sitting up in bed writing a postcard to his wife when one second later he fell forward and was dead. For a while it was thought that he died of ventricular fibrillation as a result of digitalis. This occurred before the diagnosis of coronary thrombosis was understood. Post-mortem examination revealed a fresh cardiac infarct, a rupture of the left ventricle and a large hemopericardium. Although very sudden or instantaneous death while the patient is apparently doing satisfactorily is apt to be due to rupture of the heart, that this is not necessarily the explanation was shown by cases 9 and 66. In both of these cases post-mortem examination showed typical findings of coronary thrombosis and cardiac infarction but no rupture. Sudden death might have occurred because of ventricular fibrillation or the inception of complete heart block.

Further complications that not infrequently develop shortly after the initial attack of coronary thrombosis are peripheral emboli. In many cases mural thrombi form within the ventricular cavities and remain silent only to be found when the heart is examined at autopsy. Occasionally, however, emboli are dislodged from the thrombus and reach the brain, limbs or other important organs. Death may occur

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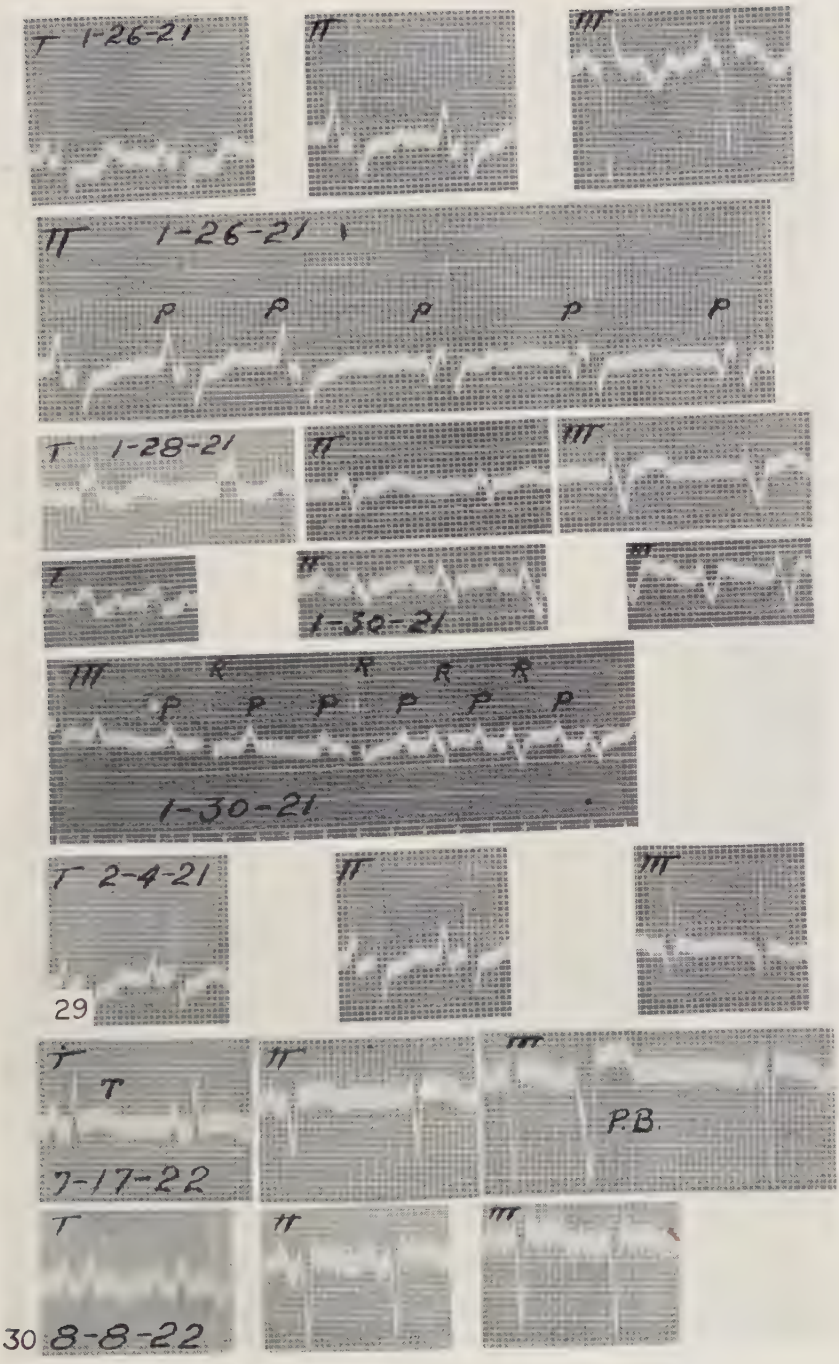
Fig. 29. Case 9. Attack January 23, 1921. Second tracing January 26, 1921 shows nodal rhythm; following two sets show defective conduction through right branch of bundle of His on January 30, 1921. There was partial heart block. Died February 7, 1921. Autopsy showed infarct of left ventricle.

Fig. 30. Case 16. Attack July 4, 1922. There is a suggestive high take off of T 1 and T 2. One premature ventricular beat is seen (P.B.). Died August 8, 1922. Autopsy showed infarct of left ventricle and rupture.


I 1-26-21
II
III
II 1-26-21
P P P P P
I 1-28-21
II
III
I
II 1-30-21
III
R R R R
P P P P P P
1-30-21
I 2-4-21
II
III
29
I
T
7-17-22
II
III
P.B.
I
II
III
30 8-8-22

FIGS. 29–30

from the accompanying gangrene of the leg and the additional burden on the patient's vitality resulting from the new infarcted blood vessel, or from a cerebral embolus with its trail of hemiplegia, unconsciousness and impariment of the function of the higher centers. Although these emboli are apt to develop during the second week of the illness we have recently witnessed an instance in which an embolus developed in the popliteal artery about 24 to 48 hours after the onset of the attack. Another case was observed where a hemiplegia occurred five weeks after the onset (case 121). Although it seems reasonable to suppose that emboli might be detached at any time, even months or years after the formation of the left ventricular mural thrombus, and no doubt explains some obscure cases of sudden hemiplegia and the like in vascular patients, nevertheless we have not seen any occur in direct relation to an attack after the sixth week. From the practical point of view this is of some importance in estimating the length of bed rest that should be carried out.

There is finally a group of patients who recover from the immediate effects of coronary thrombosis, but directly after this temporary improvement a progressive failure of the circulation of the congestive type develops. The heart may remain regular or after one or more spells of transient auricular fibrillation it may become permanently irregular. There develop increasing dyspnea, peripheral oedema, Cheyne-Stokes breathing, and the other evidences of circulatory insufficiency (case 55). Although even when this occurs improvement may result with proper treatment, more often the improvement is only too brief and death takes place in one to three months. In some in-

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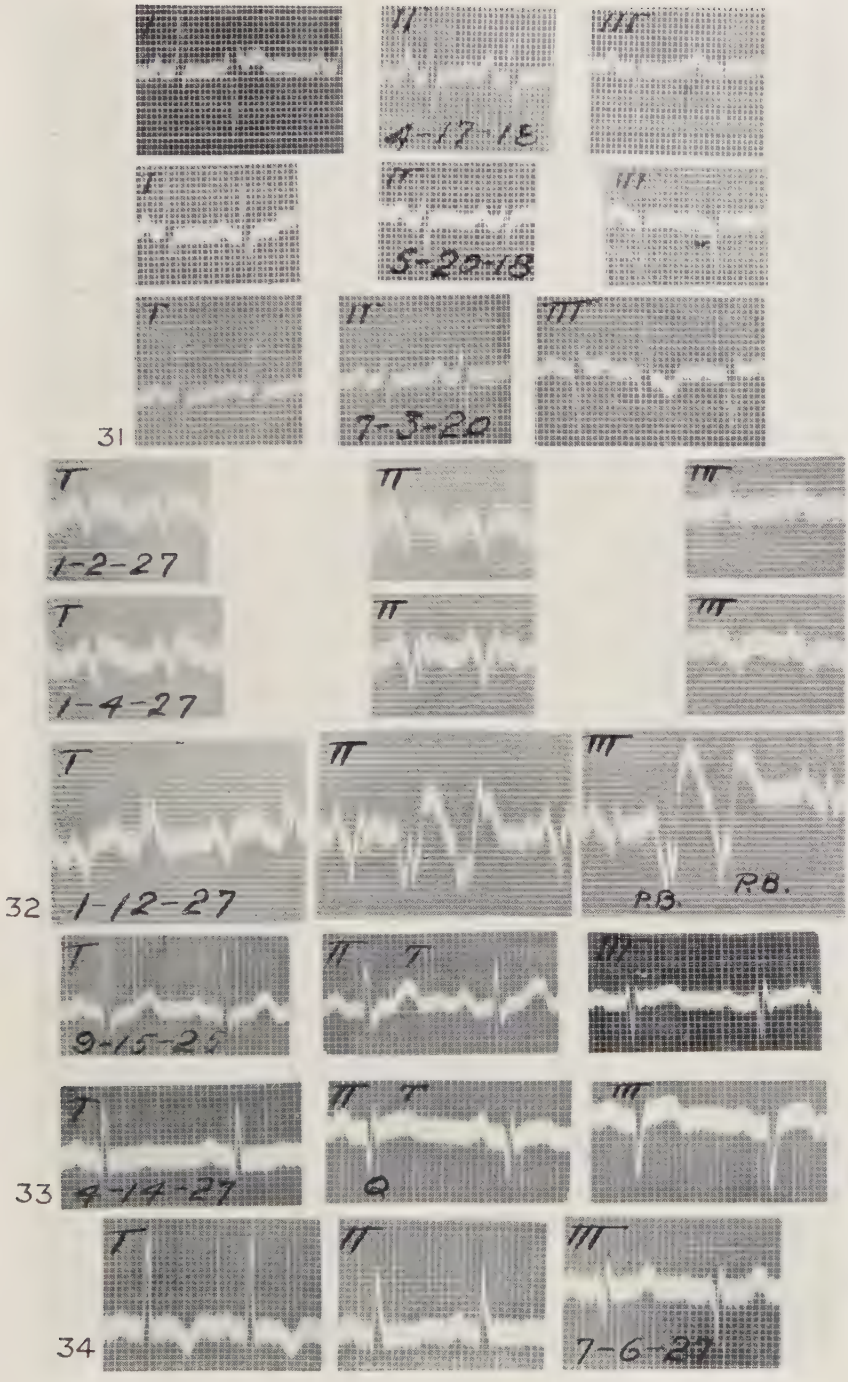
Fig. 31. Case 5. Possible date of attack May 21, 1918. Tracings merely show an occasional premature ventricular beat. Died July 14, 1918. Autopsy showed infarction of the left ventricle.

Fig. 32. Case 136. Attack December 24, 1926, or December 31, 1926. Note that the ventricular complexes were of low amplitude on the first two dates. Last tracing shows numerous extra ventricular systoles (patient had paroxysmal ventricular tachycardia). Died January 13, 1927. Autopsy showed thrombosis of left coronary artery.

Fig. 33. Case 89. Attack April 9, 1927. Note change in T wave especially in lead 2 after the attack. Patient recovered and has done well for nine months.

Fig. 34. Case 91. Attack December 13, 1926. Note slightly rounded and dipped T 1. Patient recovered and one year later had attack of acute pulmonary oedema from which he also recovered.


31
I
II
III
4-17-18
5-22-18
7-3-20
32
1-2-27
1-4-27
1-12-27
RB.
RB.
9-15-26
33
4-14-27
34
7-6-27

FIGS. 31–34

stances a fair degree of cardiac strength is restored, the patient becomes ambulatory, remains free from pain, and carries on with a limitation in his activities for years. It is in this last group of ambulatory patients that instances of true aneurysms of the ventricles are found.

k. Types of recovery

It is of considerable importance to appreciate that patients who recover from an attack of coronary thrombosis differ considerably as to their future health entirely apart from the actual duration of life after such an attack. In general there are three types of recovery that are fairly distinct and quite different from each other. One common type is that illustrated by cases 40 and 42. Here the patients were suffering from typical angina pectoris for a variable period of time before the attack of coronary thrombosis. With the attack there was a well marked fall in the blood pressure which with recovery remained at a distinctly lower level thereafter. In these cases when the patients became ambulatory the angina pectoris did not return. This type illustrates the most favorable kind of recovery for the patients are in some ways in better health after than before the attack. It follows that a marked fall of blood pressure is a welcomed sign if it does not rise again to the previous level as recovery takes place. There are several such patients who are quite well and active three to five years after their attacks.

A second group of cases illustrated by cases 65, 111 and 135 is one in which angina symptoms, whether existing before the attack of coronary thrombosis or not, are present after it. In such cases either the fall of blood pressure did not occur, was slight, or if it was considerable it rose again to a high level after the attack. Here the patients present the ordinary problem of angina pectoris which limits their activities to some extent. This one might regard as the next most favorable type of recovery.

The last major group consists of those who develop greater or lesser

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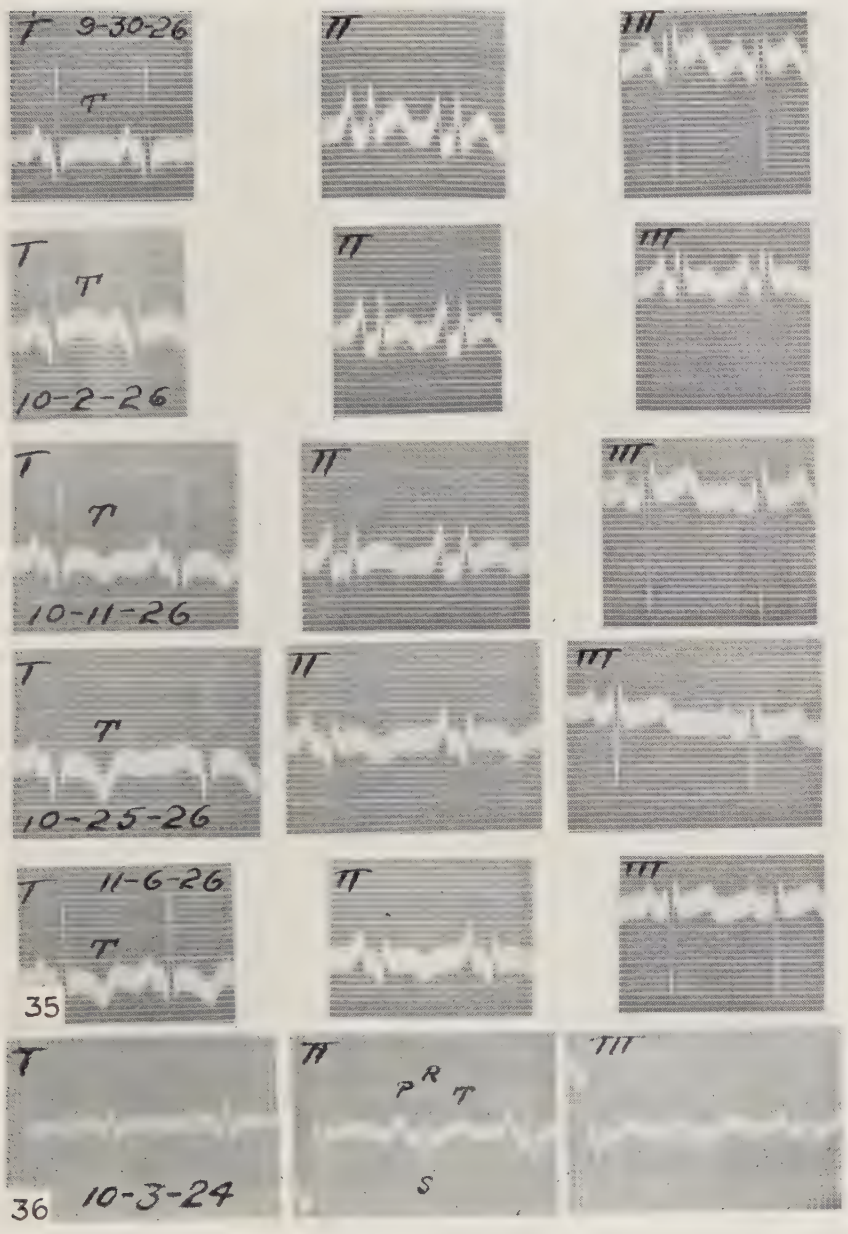
FIG. 35. Case 67. Attack September 27, 1926. Note the changes in T wave especially in lead 1. Patient recovered, became ambulatory but suddenly died March, 1927.

FIG. 36. Case 42. Attack June 21, 1924. Standardization shown at beginning of each lead. Note the low amplitude of the Q R S waves. Patient has done well for past $3\frac{1}{2}$ years.


I 9-30-26
T
II
III
I
T
10-2-26
II
III
I
T
10-11-26
II
III
I
T
10-25-26
II
III
I 11-6-26
T
35
II
III
I
36 10-3-24
II
P R T
S
III

FIGS. 35–36

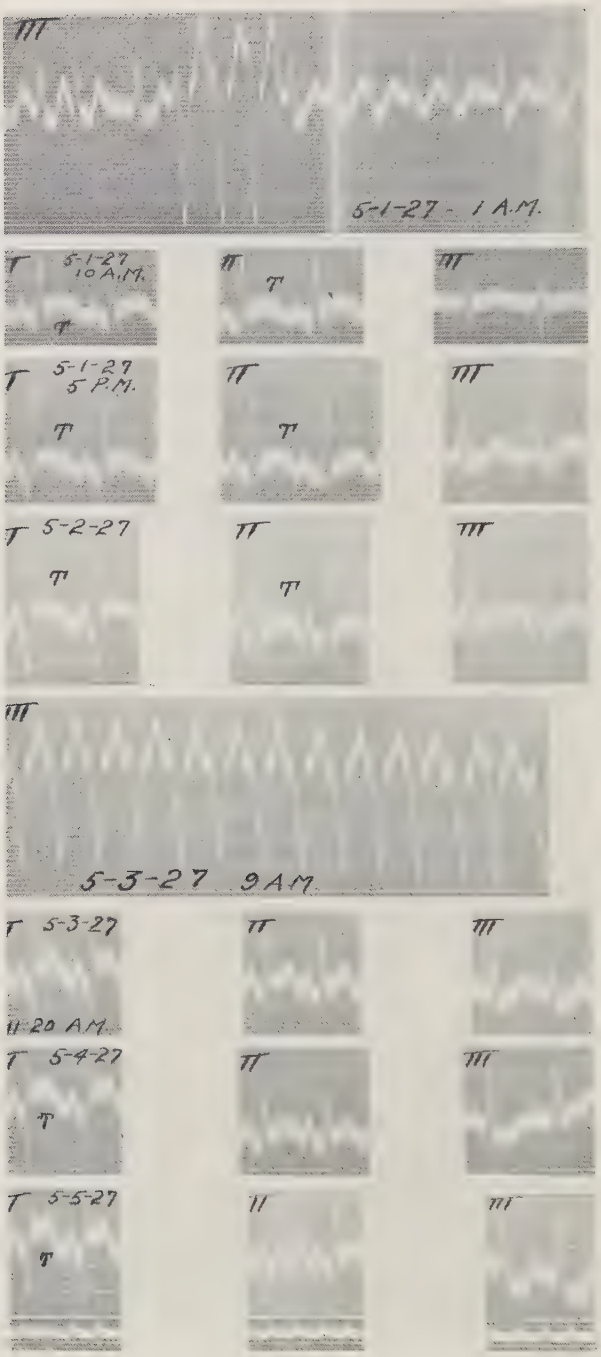


FIG. 37. Case 141. Attack April 27, 1927. Note the high take off of T 1 and T 2. First tracings show both a transient auricular fibrillation and frequent extra ventricular systoles. On May 3, 1927, ventricular tachycardia developed which was readily controlled by quinidine. Tracings taken 11:20 a.m. (two hours and fifteen minutes after 0.4 gram quinidine was given) show normal rhythm. Died May 7, 1927. Autopsy showed rupture of left ventricle.

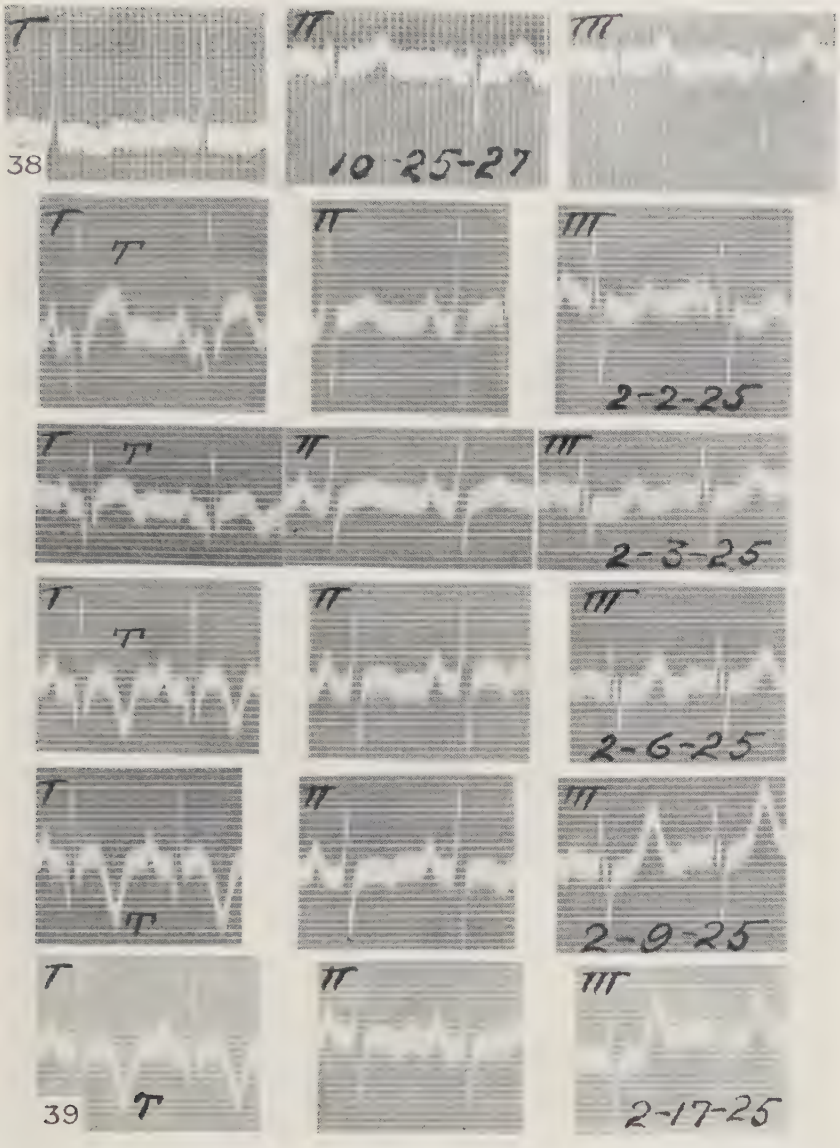


FIG. 38. Case 93. First attack July, 1925; second attack July, 1927. There is nothing remarkable in the electrocardiogram. Patient has mild anginal attacks, but has survived two major attacks.

FIG. 39. Case 34. Attack January 27, 1925. Note the high take off of T, and the progressive and rapid changes in the form of the T wave first being rounded and then having the typical V-shaped inversion. Patient had an immediate recovery, but the ultimate outcome is not known.

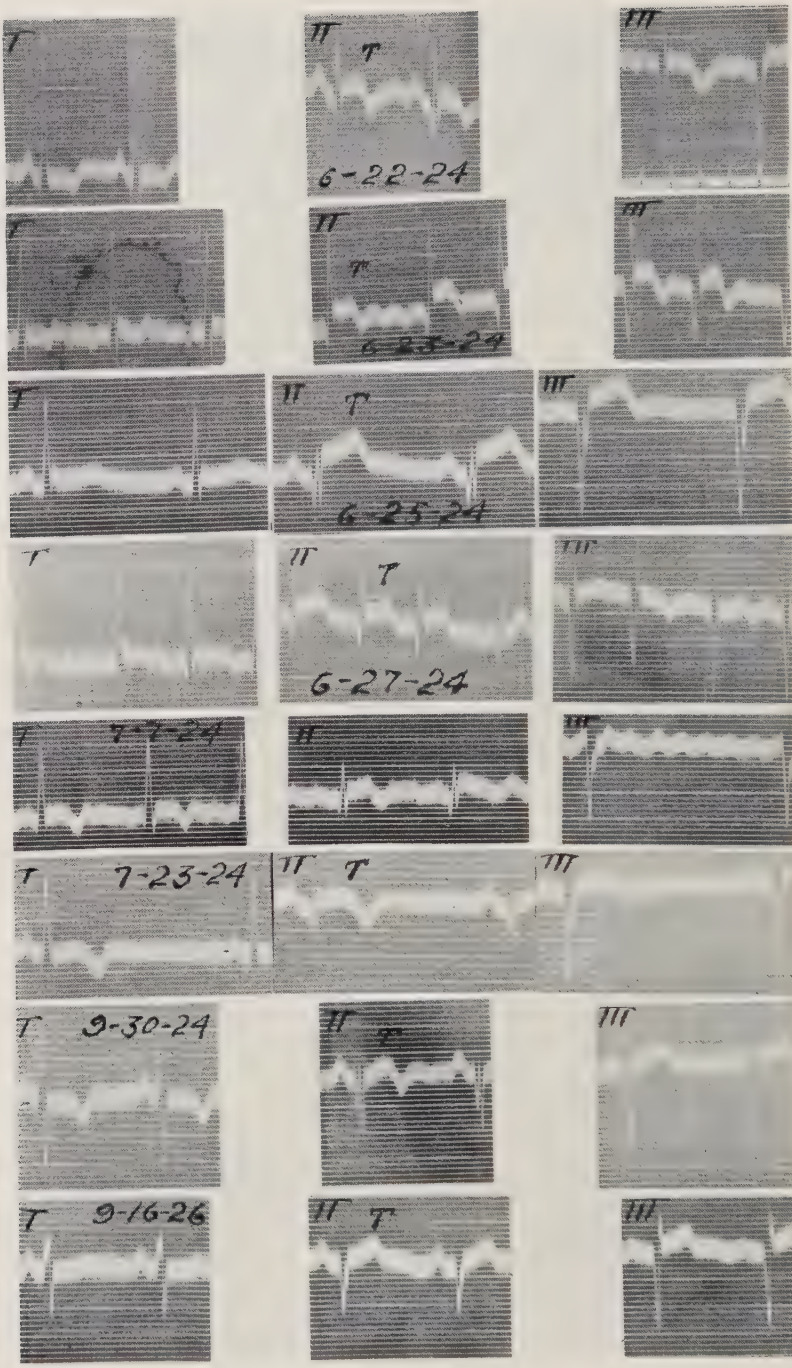


FIG. 40. Case 28. Attack June 17, 1924. Note the high take off of T 2 and T 3. Transient auricular fibrillation occurred on June 23, 1924; June 27, 1924, and July 7, 1924. A prominent Q 3 developed, and the T waves changed form from time to time. Died February 6, 1927. Autopsy showed old infarct of left ventricle with localized aneurysm of the wall.

evidence of general circulatory insufficiency after an attack of coronary thrombosis (cases 28, 55 and 81). They may have had no such symptoms before the attack and in fact during the early critical days of acute thrombosis they might show no signs or symptoms that are different from those manifested by the first group, and yet as the days or weeks progress it becomes increasingly clear that the circulation is insufficient; dyspnea, oedema, enlarged liver and hydrothorax develop which may or may not respond to the customary measures employed under such circumstances. In this group persistent auricular fibrillation may be found. Dyspnea, congestion of the liver and lungs,

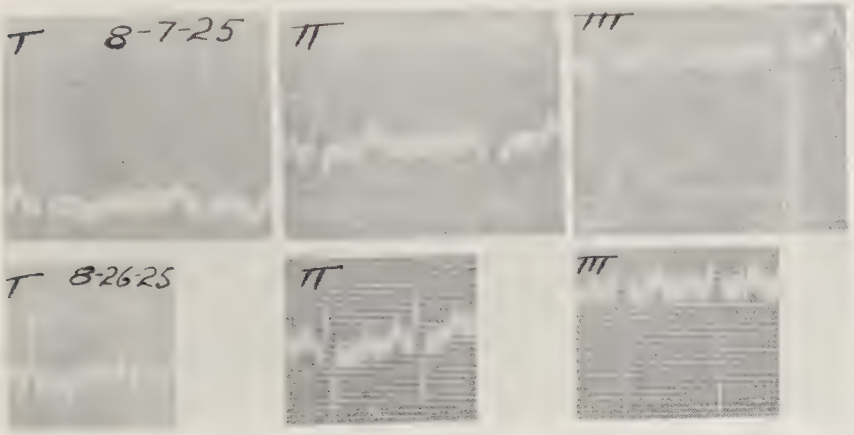


FIG. 41. Case 58. Attack August 25, 1925. The height of the ventricular complexes diminished somewhat after the attack, but the form was hardly changed. Died August 31, 1927. Autopsy showed syphilitic aortitis and acute infarction of left ventricle.

Cheyne-Stokes breathing, and the like when occurring during the first few days, although evidence of an insufficient circulation, by no means indicate that the patient will belong to this third group when recovery takes place. They are frequently only temporary and patients showing these signs commonly recover most satisfactorily and fall into the first group. When such symptoms are present a few weeks following an attack they have a more ominous significance. There will be an occasional instance in which recovery takes place after a cerebral embolus occurred, and here, obviously, the patient will be left with a hemiplegia or the like.

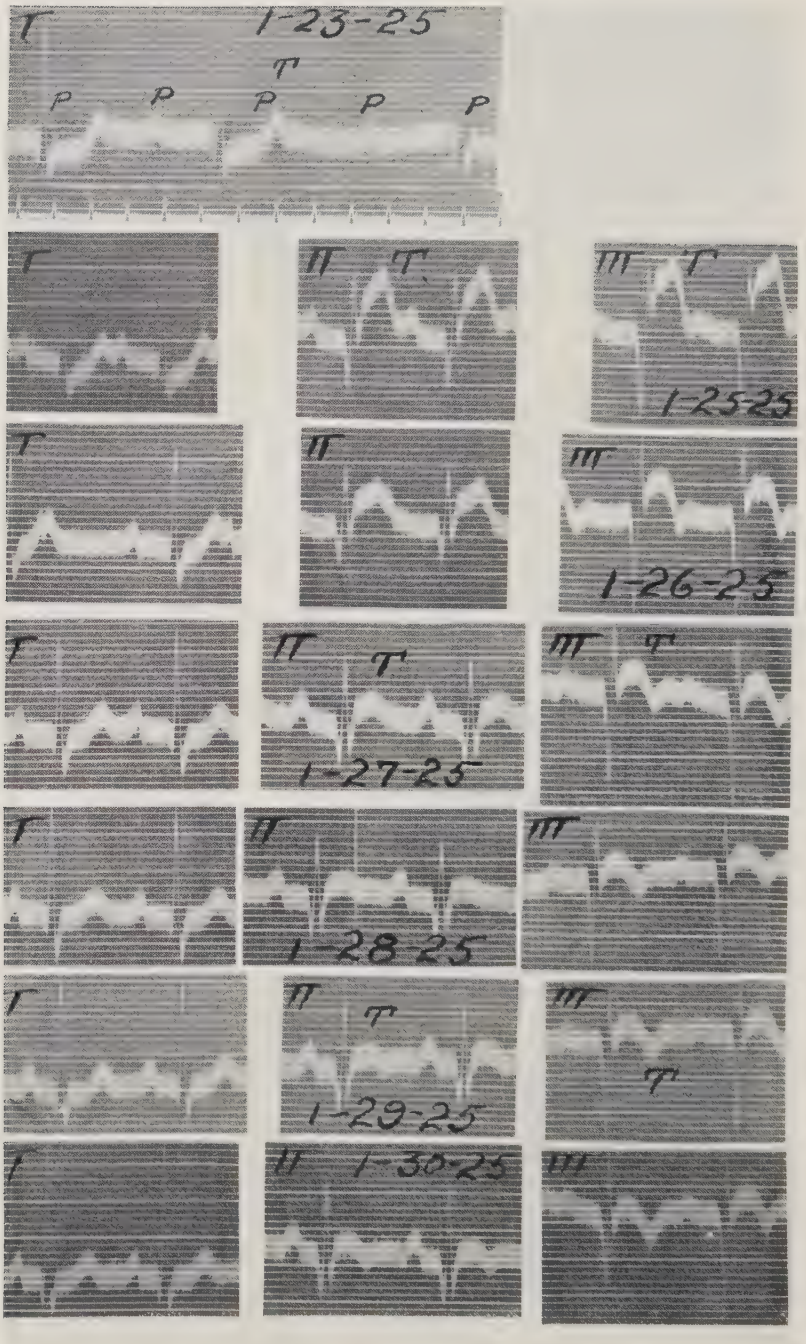


Fig. 42a

Fig. 42 (a and b). Case 35. Attack January 22, 1925. Tracings show striking progressive changes in the form of the ventricular complexes from an extremely high take off on January 25, 1925, to a marked inversion February 20, 1925. Partial heart block is

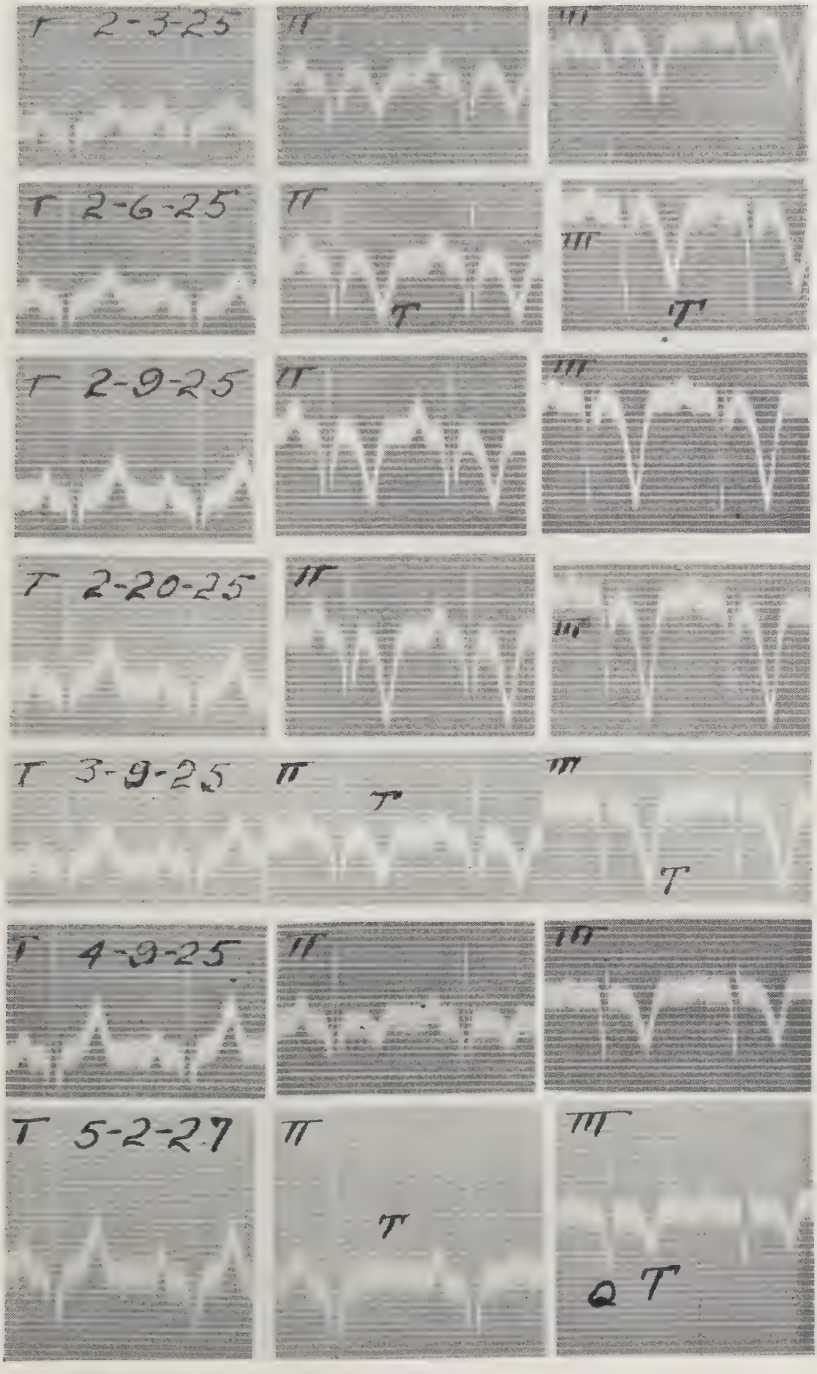


FIG. 42b

shown on January 23, 1925, and January 26, 1925. These curves illustrate different types of electrocardiograms one might obtain at different days after an attack. Patient has been at work for past 3 years.

There is in addition a heterogeneous group which may continue to have anginal attacks of pain and still show evidence of congestive heart failure of varying degree; or as happens occasionally, a patient who

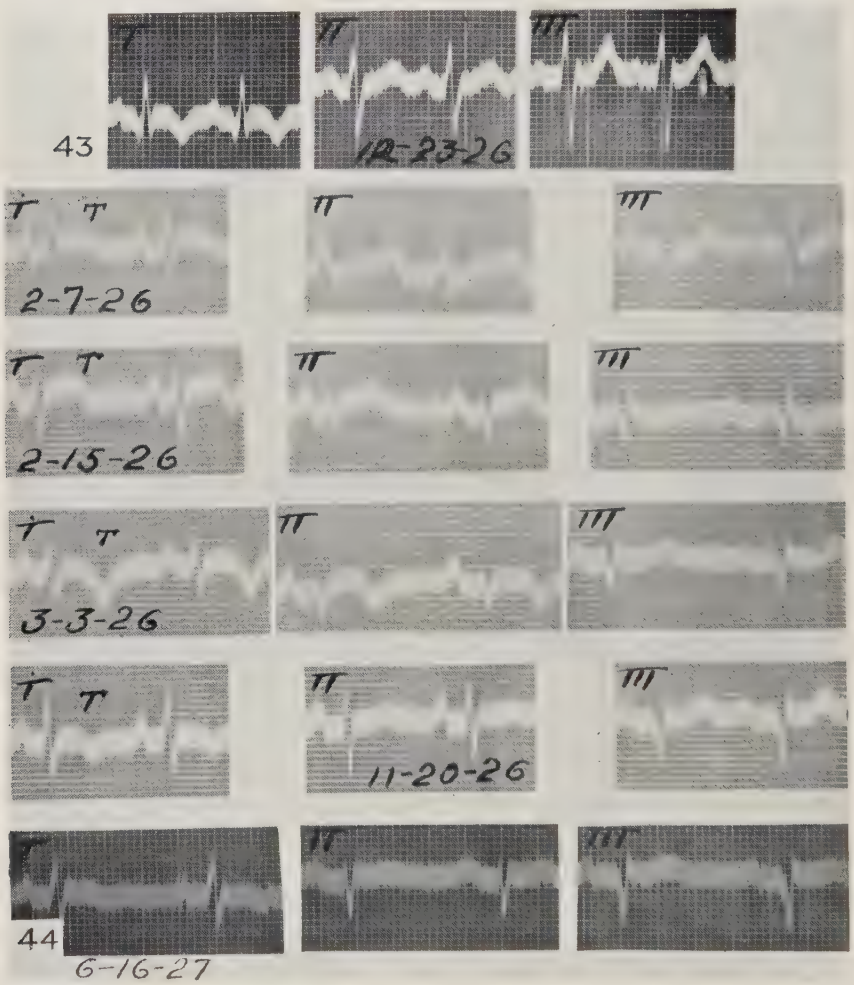


Fig. 43. Case 102. Attack November 26, 1926. T 1 has the characteristic rounded dipped form. Died February 11, 1927.

Fig. 44. Case 69. Attack February 4, 1926. Note slight but significant changes in the T waves, the low amplitude of Q R S waves, and the presence of a Q 3. Patient recovered and has had no symptoms for 1 year.

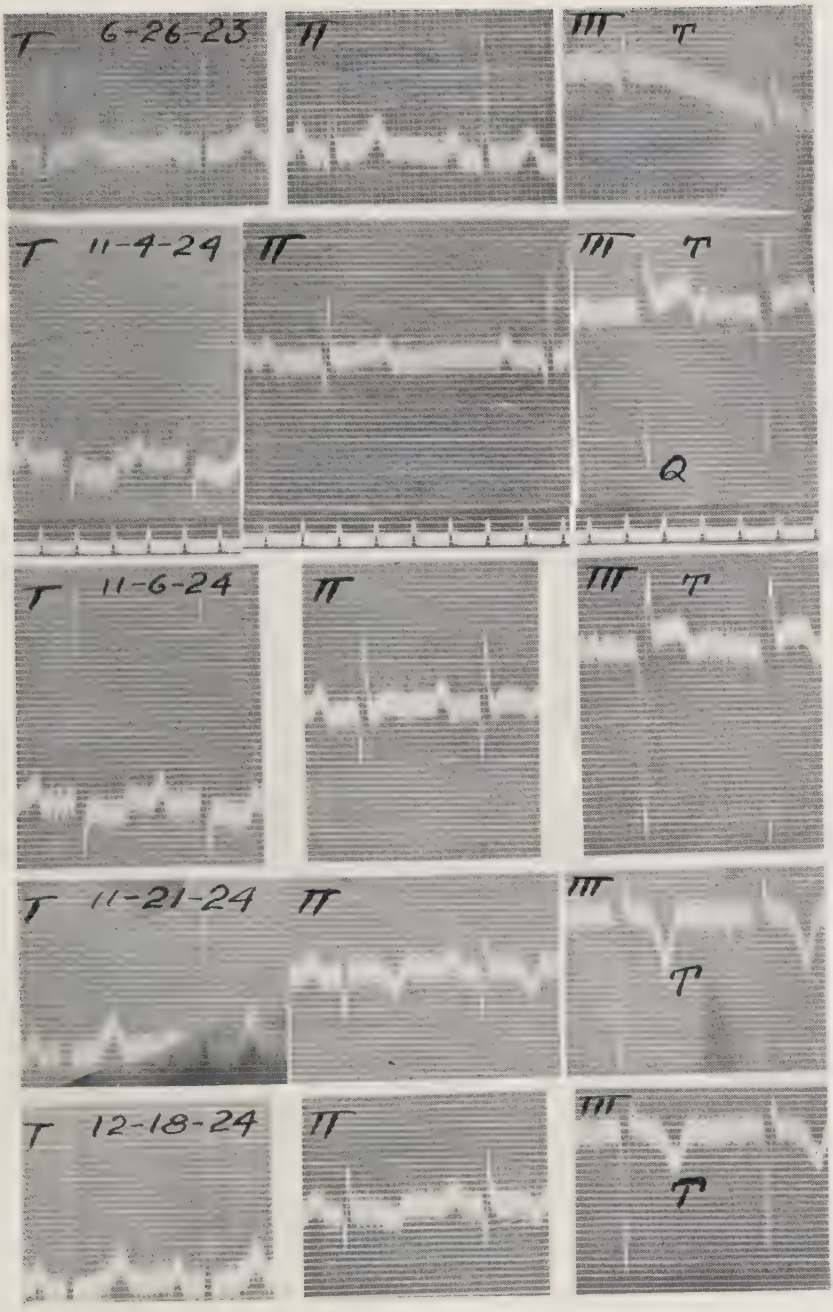


FIG. 45. Case 32. Probable date of attack October 28, 1924. Note the changes in the T waves. On November 4. 1924, partial heart block appeared. Patient recovered and then died in the spring of 1927.

was free from angina pectoris for some time after an attack may then develop either pain or dyspnea or other symptoms of an insufficient circulation. Obviously a more prolonged study of the recovered cases will disclose new developments. Those who are now free from pain and well may develop congestive heart failure or angina pectoris in the future, or those who still have anginal attacks may have another attack of coronary thrombosis which, if not fatal, may serve to render the patient free from further pain. Notwithstanding these aberrations the general division into the above three groups will be applicable in most cases.

l. Electrocardiographic changes

Although the recognition of cases of coronary thrombosis developed as a bed side or clinical diagnosis before the use of electrocardiography was generally made, this latter procedure has in recent years added materially to the criteria that we use in diagnosis. In fact, certain changes that occur in the electrocardiograms are now regarded as so characteristic that without any other evidence whatever a proper diagnosis might be made in some cases. Other changes have also come to light that are less distinctive but nevertheless decidedly helpful when coupled with further clinical data. Altogether electrocardiographic data as will be seen below are now of great importance both in the diagnosis of coronary thrombosis during the acute stage of the disease, and in some instances enabling us to detect even a previous attack of coronary thrombosis that occurred in the past from which the patient recovered.

Wearn (22) studying some of the cases reported in this review, called attention to diminution in the amplitude of the electrocardiographic waves in two of his patients. This has been observed by others since his publication, and in some of our patients marked diminution of the

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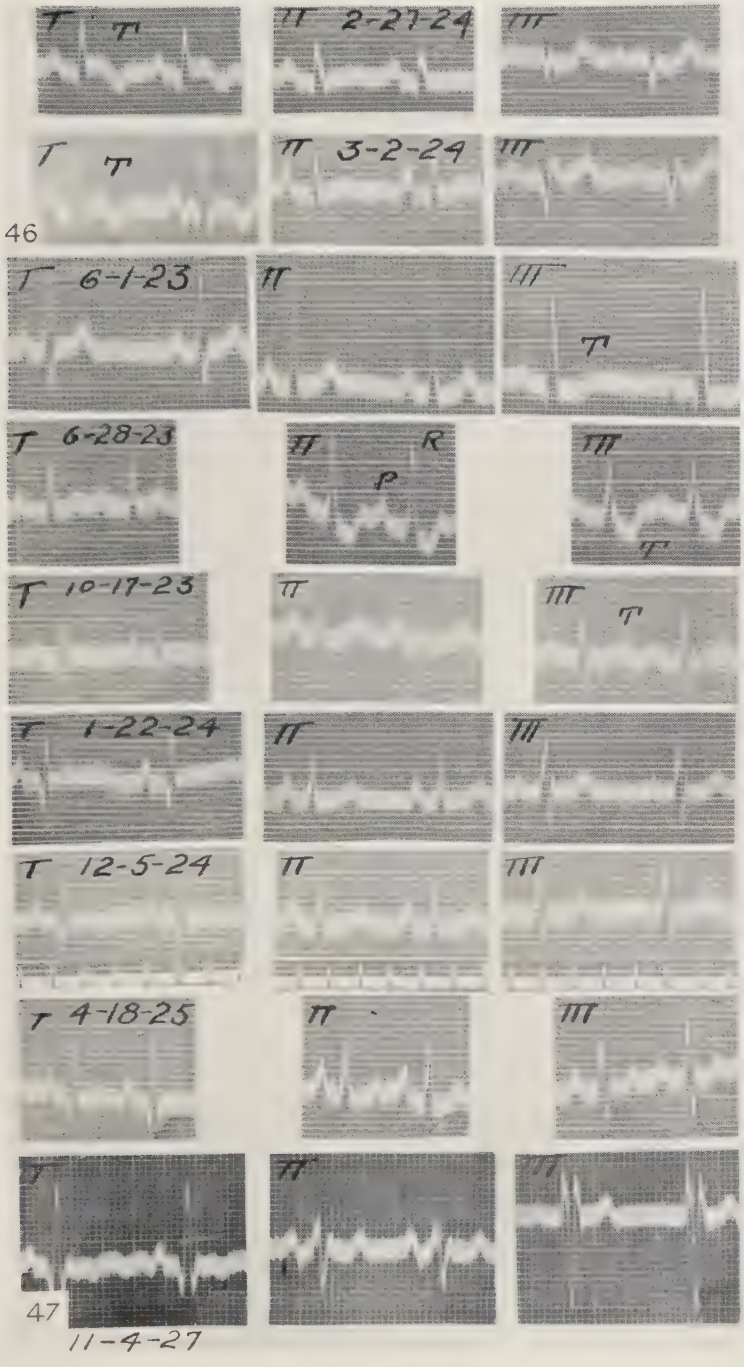
FIG. 46. Case 24. Probable date of attack February 3, 1924. Note the high take off of T 1 which later becomes rounded. Patient recovered but died instantly February, 1925.

FIG. 47. Case 40. First attack June 25, 1923. Second attack January, 1928. Note changes in the form of the T wave. On June 28, 1923, there was distinct delayed A-V conduction, as indicated by an increased P-R interval. Patient survived a second attack in 1928.


I
II 2-27-24
III
I
II 3-2-24
III
46
I 6-1-23
II
III
I 6-28-23
II R
P
III
I 10-17-23
II
III
I 1-22-24
II
III
I 12-5-24
II
III
I 4-18-25
II
III
I
II
III
47
11-4-27

FIGS. 46–47

complexes has been noted (figs. 10, 11, 12, 28, 36 and 64). This is fairly valuable evidence but should not necessarily be considered pathognomonic. The most important type of change in the electrocardiogram is the one discovered by Pardee (39). He noted that during the early days following an attack of coronary thrombosis the form of the complex between the downstroke of the R wave and the end of the T wave changes. This change consists of the disappearance of the brief iso-electric interval that normally exists between the Q-R-S complex, or initial ventricular deflection, and the T wave or terminal ventricular deflection. Furthermore, the T wave begins on the downstroke of the R wave before it has reached the base line and has a peculiar rounded hump. Whereas this may be detected in one of the three customary leads taken in routine tracings, an opposite change which seems to us to be equally significant may be seen in one of the other leads. This is a low take-off of the T wave from the upstroke of the S wave before it has returned to the base line. When such changes in the R-T interval are marked (see fig. 42) they are practically pathognomonic of coronary thrombosis. One other clinical condition that shows slightly similar changes but not to such a marked extent is that of acute rheumatic fever, and was described by Cohn and Swift (66). Here although the iso-electric R-T interval may be absent, the T waves does not rise from as high or low a point on an R-S wave as is found in coronary thrombosis (fig. 84). Somewhat similar changes have been noted in other conditions, namely uraemia and pneumonia (figs. 83 and 85), but on careful examination it will be seen that the similarity is not great for the T waves do not have that peculiar rounded hump that is found in coronary thrombosis. Although abnormal electrocardiograms have been described in uraemia (67), they generally can be distinguished from the changes discussed here.

The above changes may occur very early in the attack, even a few hours after the onset, as was shown by Rothschild, Mann and Oppenheimer (44), but they may develop more slowly and be absent the

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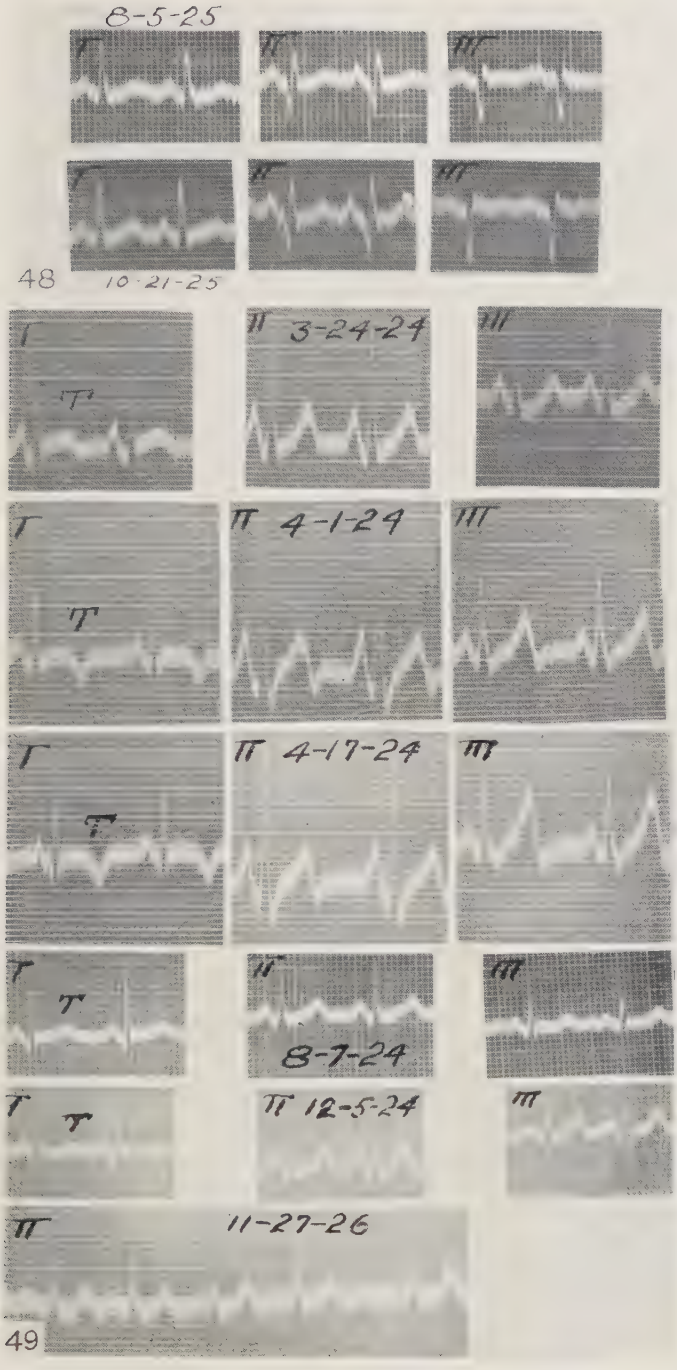
Fig. 48. Case 103. Attack March 1, 1925. There is nothing striking in these electrocardiograms.

Fig. 49. Case 41. Attack March 21, 1924. Note the curved and dipped form of T 1 in the early tracing. Two and one-half years after the attack permanent auricular fibrillation set in.


8-5-25
I
II
III
I
II
III
48
10-21-25
I
T
II 3-24-24
III
I
T
II 4-1-24
III
I
T
II 4-17-24
III
I
T
II
8-7-24
III
I
T
II 12-5-24
III
II 11-27-26
49

FIGS. 48–49

first day and appear later (fig. 66). They occur in a great many of the cases, but by no means in all, so that their absence does not rule out the diagnosis of coronary thrombosis. A further important feature

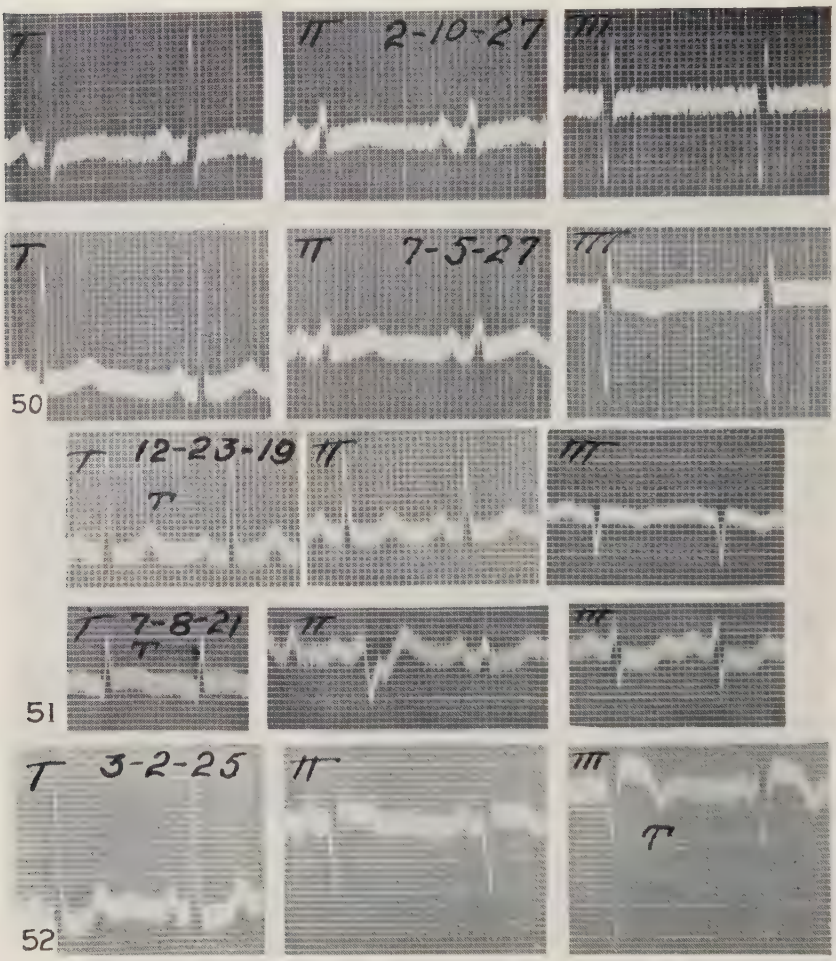


Fig. 50. Case 104. Attack October 30, 1926. There is nothing remarkable except the prominent Q 3.

Fig. 51. Case 10. Attack July 7, 1921. Note that the T wave in lead 1 after the attack comes off at a slightly higher level than normal. Patient died suddenly July 8, 1921, and autopsy showed a ruptured heart.

Fig. 52. Case 36. Attack February 22, 1925. Note the high take off and rounded dipped T 3. Patient died March 2, 1925. Autopsy showed a rupture of the left ventricle.

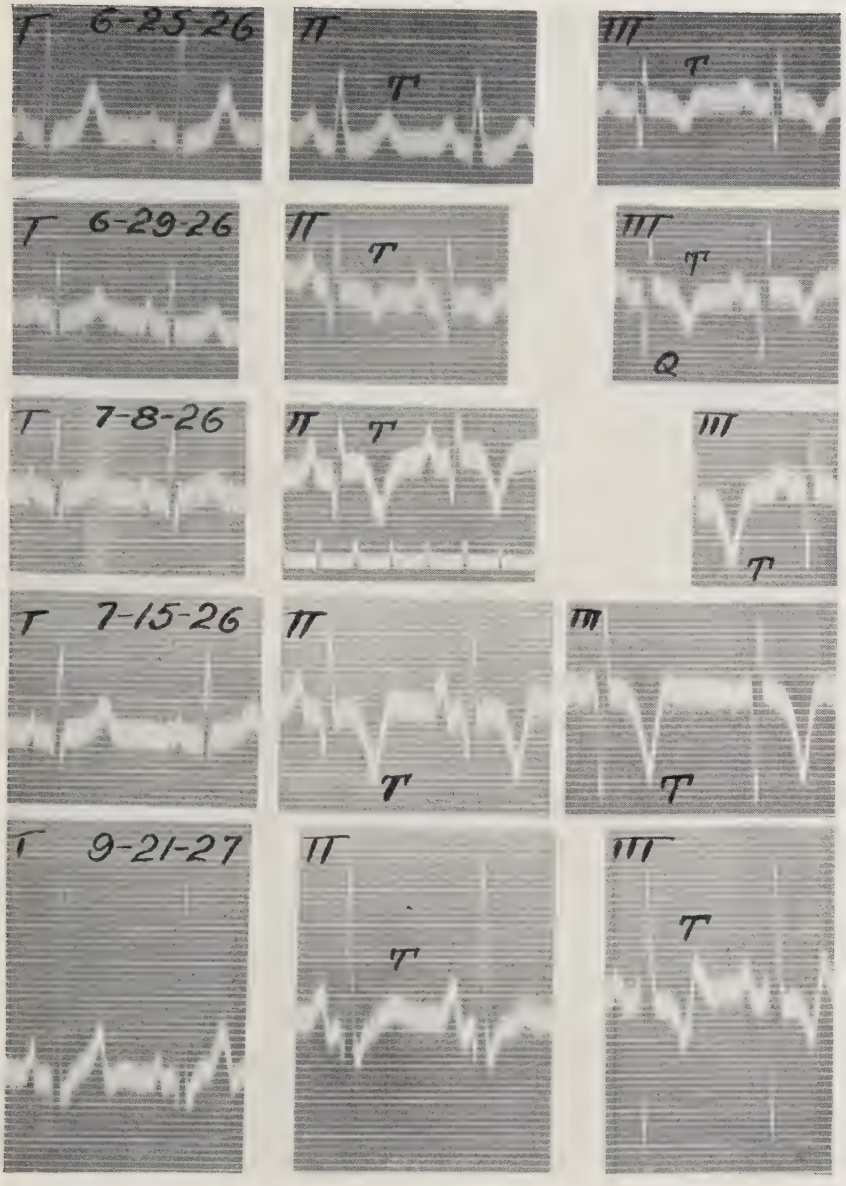


FIG. 53. Case 65. Attack June 23, 1926. Note the striking changes in the form of the T waves, also the prominent Q 3.

of the electrocardiogram is the fact that the complexes change their form from day to day. There is practically no other condition in which the form of the electrocardiogram changes materially from day to day, or at least goes through such significant changes so quickly as occurs in coronary thrombosis. One can frequently see the R-T complex which showed the characteristic high take-off and rounded hump on one day go through changes like those shown in figure 42. The T wave gradually recedes from its high position, still maintaining its rounded contour and then develops a peculiar sharp inversion, at first slight, and then more prominent. Finally it may appear as a very sharp inverted V-shaped curve. These changes are of considerable importance as frequently the first tracing obtained is one taken some days or weeks after the onset of a suspected attack, and one is thereby enabled to infer that the earlier changes had occurred but were not photographed, and that because the later characteristic curves are obtained the patient probably had an attack of thrombosis some time in the past and has now recovered from it (figs. 22 and 43).

Attention has been called to a very slight notch or wave that occurs in the early portion of the R-T interval, as the changes above described are taking place. This has been noted in some of our cases (fig. 81), but its frequency has not been sufficiently great or its identity sufficiently characteristic for us to feel that it has an important diagnostic significance.

A final feature in the electrocardiograms that we have found to be of some importance, and to which no attention has in the past been paid, is the presence or the development of prominent Q waves in lead 3.

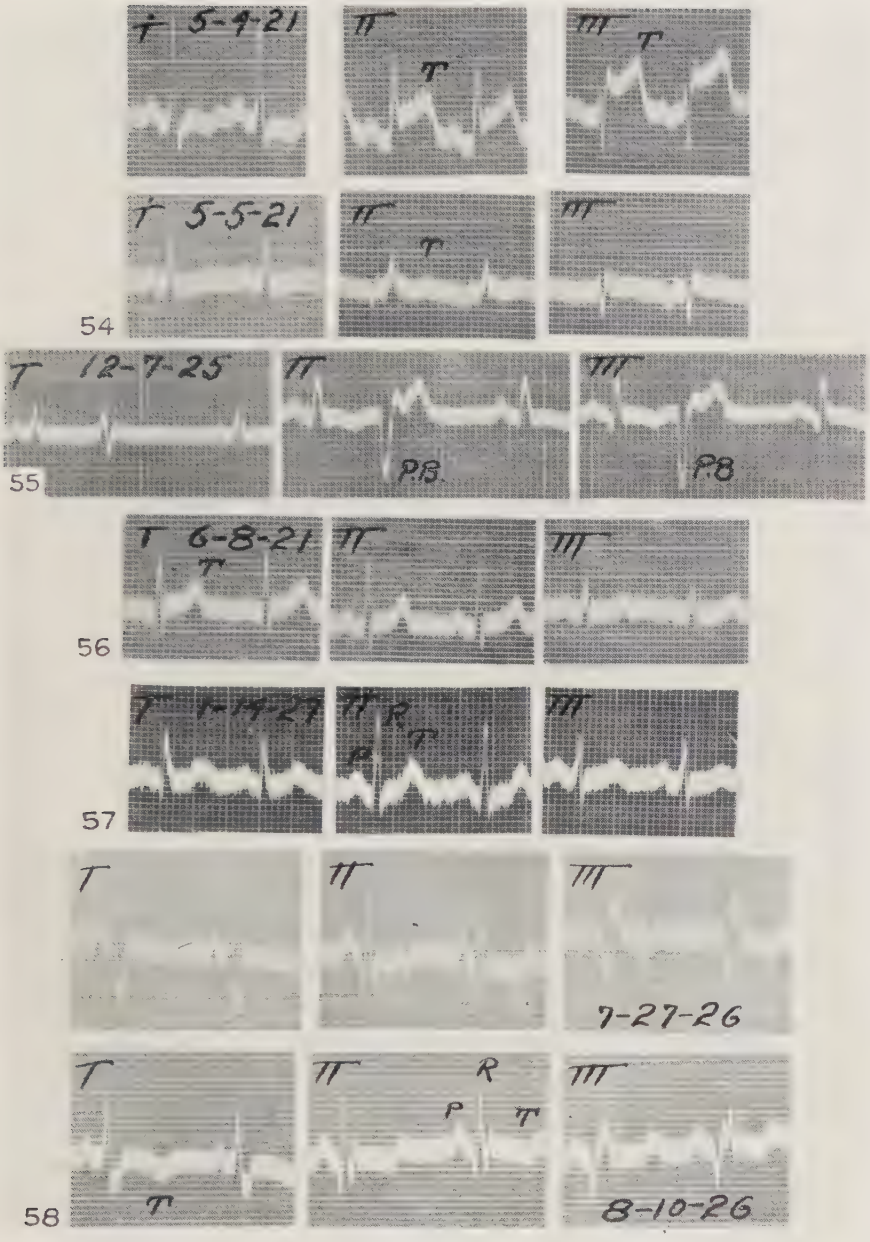
Fig. 54. Case 138. Attack April 26, 1921. Note the extremely high level at which T 2 and T 3 begin. The following day these changes had disappeared. Patient died May 10, 1921, and autopsy showed a rupture of the left ventricle.

Fig. 55. Case 105. Attack November 24, 1925. Note the frequent premature ventricular beats (P.B.). Patient recovered satisfactorily.

Fig. 56. Case 145. Attack June 8, 1921. Note the suggestive high take off of T 1. Patient has done well for almost 7 years.

Fig. 57. Case 106. Attack December 16, 1922. The curves are essentially normal Patient recovered very well.

Fig. 58. Case 66. First attack March, 1926; second attack probably July 12, 1926 Note the spread and notching of the Q R S waves, and the slight dipping in T 1. Patient died suddenly August 17, 1926. Autopsy showed thrombosis of right and left coronary arteries. There was evidence of an old and a recent cardiac infarction.


I 5-4-21
II
T
III
T
I 5-5-21
II
T
III
54
I 12-7-25
II
P.B.
III
P.B.
55
I 6-8-21
T
II
III
56
I 1-14-27
II
R
P
T
III
57
I
II
III
7-27-26
I
T
II
R
P
T
III
8-10-26
58

FIGS. 54-58

The exact significance of this is obscure, but its frequent appearance in this group of patients has been sufficiently great to require some comment. It is hardly likely that such curves can be regarded as accidental (figs. 7, 9, 22, 24, 26, 40, 42, 45, 53, 59, 65, 66 and 79). There are of course many other electrocardiographic abnormalities that occur in this disease, but they are no different from those observed in other patients with degenerative myocardial disease who have not had coronary thrombosis. Such changes are bundle branch block, or evidence of intraventricular defective conduction as indicated by lengthening of the duration of the Q-R-S complex. In fact, one must be cautious in interpreting the abnormal electrocardiogram, properly assigning certain changes to the chronic process in the heart muscle and other changes to the more acute events that follow coronary thrombosis.

IV. DIFFERENTIAL DIAGNOSIS

The most common difficulty in diagnosis that arises is to distinguish an attack of coronary thromobosis from one of angina pectoris. In most cases this can be done with a fair degree of certainty, while occasionally one will remain in doubt until one of the more critical and characteristic features of the disease is noted. At times it will be impossible to be certain just how seriously the condition should be regarded and judgment will need to be held in abeyance. The important differences are the duration and severity of pain which in angina pectoris lasts minutes and in coronary thrombosis hours or days. In the one relief is generally obtained by using nitroglycerin, in the other no such prompt relief is obtained using nitrites or even morphia. The gradual fall in blood pressure, the increase in the heart rate, the leucocytosis, the fever, the various irregularities of the heart, the occasional pericarditis, the embolic phenomena, the evidence of shock, collapse and congestive failure, and the development of dyspnea and

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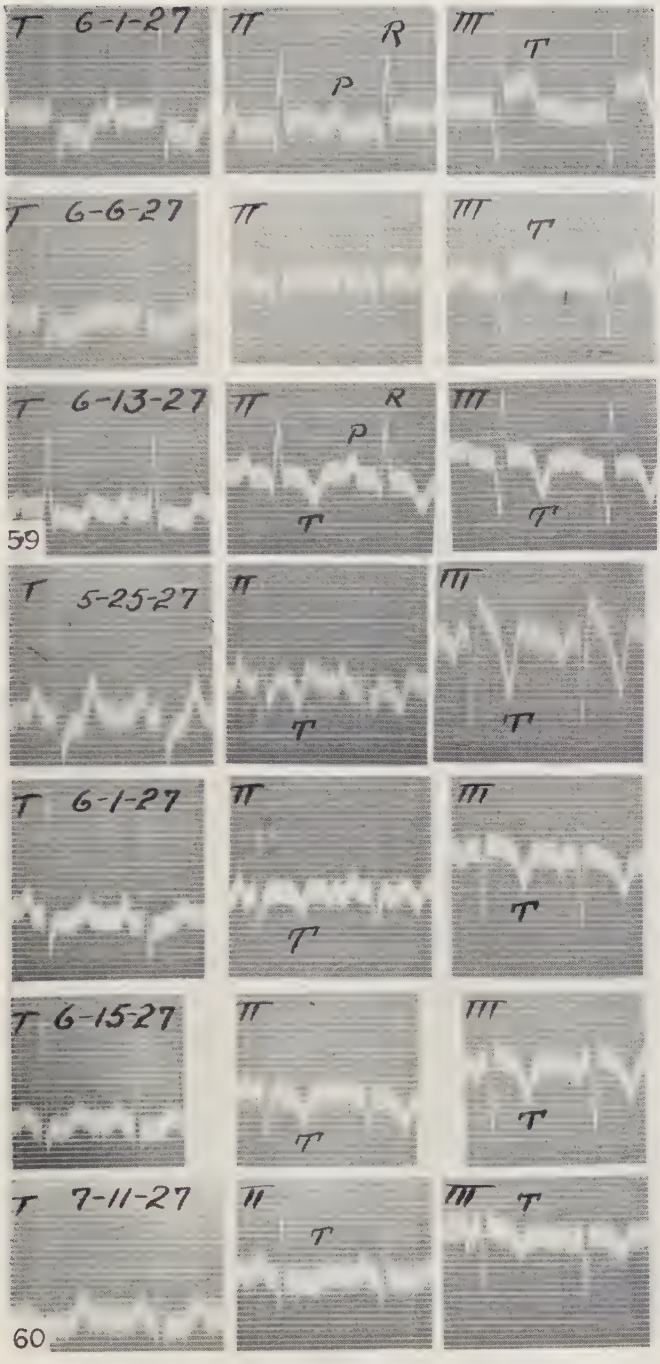
Fig. 59. Case 139. Attack May 26, 1927. The three important features here are the progressive changes in the T waves, especially in lead 3 from the characteristic high take off to the sharply inverted V-shaped form, the delayed P-R interval gradually disappearing and the prominent Q 3. This patient died July 7, 1927.

Fig. 60. Case 142. Attack May 13, 1927. Note the progressive changes in the T waves especially in lead 2. Patient recovered satisfactorily.


I 6-1-27
II
R
P
III
T
I 6-6-27
II
III
T
I 6-13-27
II
R
P
T
III
T
59
I 5-25-27
II
T
III
T
I 6-1-27
II
T
III
T
I 6-15-27
II
T
III
T
I 7-11-27
II
T
III
T
60

FIGS. 59 60

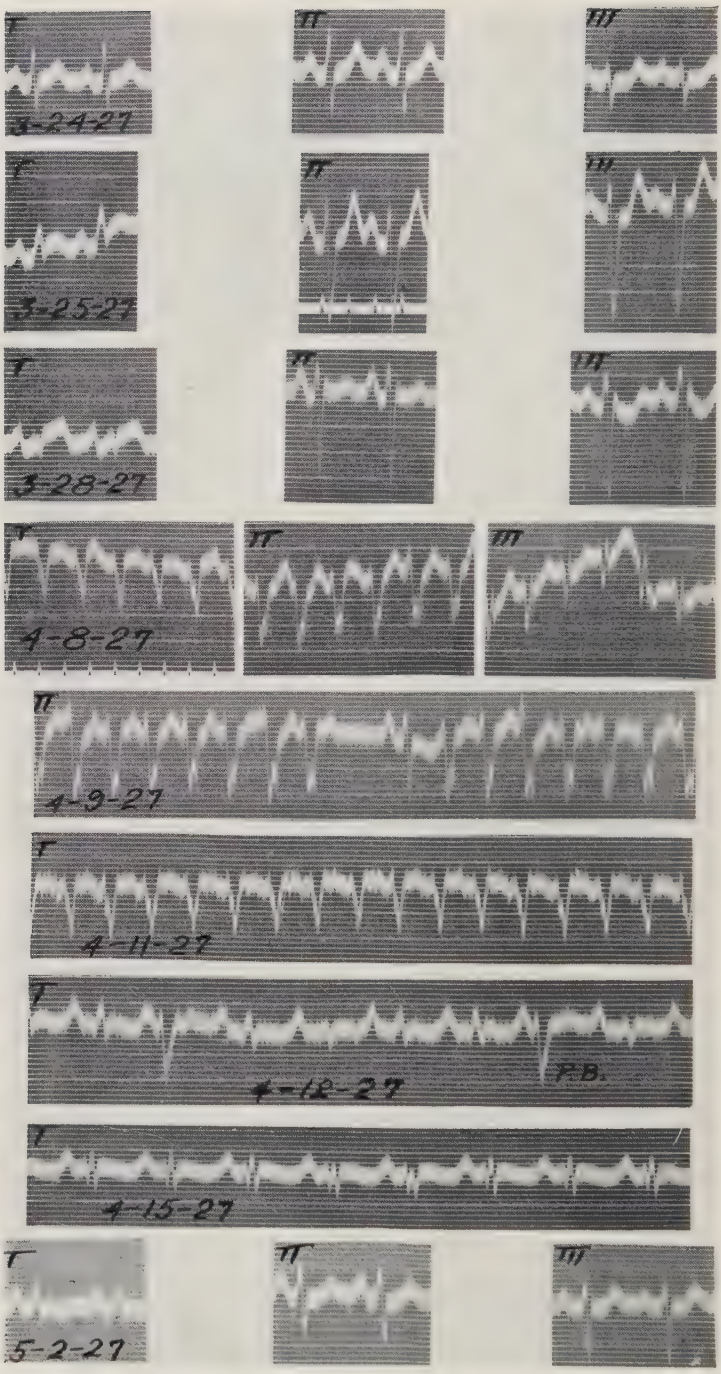


FIG. 61. Case 133. Attack March 20, 1926. The first tracings were taken 5 hours after onset. The striking phenomenon here is the development of ventricular tachycardia (April 8, 1927). The next three tracings show the gradual return to normal following quinidine. Patient recovered satisfactorily.

gastric symptoms are all events which occur with varying frequency and characterize coronary thrombosis quite satisfactorily.

There are several other conditions that may be confused with coronary thrombosis and require special mention. Of considerable importance is the small group of patients who present a picture simulating an acute surgical condition of the abdomen. This was discussed in detail above, and here let it suffice to emphasize that in all patients about the age of 40 who have acute fulminating pain in the upper abdomen, the possibility of coronary thrombosis should be considered. Eliciting a previous history of angina pectoris, uncovering the fact that although the pain is mainly in the epigastrium there is also a feeling of constriction in the sternum, or a squeezing ache in the arms or the presence of some dyspnea during the attack, may lead one to make an accurate diagnosis. At other times, where possible, electrocardiograms or suspicious findings on ausculating the heart may save the patient from an unnecessary and perilous operation. In fact, there will be times when only after a most careful survey of all the features of coronary thrombosis will the correct diagnosis be made.

Other conditions that may be confused with coronary thrombosis are diabetic acidosis, pneumonia, and rarely pneumothorax. On several occasions the appearance of sugar in the urine, even with a real acidosis as manifested by a depressed CO_2 combining power of the blood, together with the evidence of shock and stupor, have made physicians think that the patient had diabetic coma (cases 49, 53 and 68). For entirely other reasons, one might easily make the mistaken diagnosis of pneumonia and overlook the real condition (cases 8, 11, 29 and 43). This is not surprising when one recalls that the pain in the chest, dyspnea, cough, râles at one or both of the bases of the lungs, fever, and leucocytosis, are characteristic of both conditions. Of course the location of the pain is generally in the sternum, and is constricting in character, on the one hand, and is more apt to be lateral and aggravated by breathing, on the other hand. Furthermore, changes in the mechanism of the heart in pneumonia are rare, except for the occasional development of auricular fibrillation. Other evidence pointing to arterial disease, such as hypertension or angina pectoris, will aid in the diagnosis. It must be borne in mind that on rare occasions changes somewhat similar to those that occur in coronary thrombosis are found in the electrocardiograms during pneumonia (fig. 85).

There is a group of cases in which the early symptoms of the acute stage are so mild that they are disregarded and present themselves as medical problems only after an embolus has occurred, particularly when a hemiplegia results (case 20). Some cases that are diagnosed cerebral hemorrhage really fall into this group. The possibility that a hemiplegia might be due to a dislodged embolus from a left ventricular mural thrombus following a coronary thrombosis, should always be considered when it is observed in a patient who has a low blood pressure. Here also a consideration of all the various points taken up under diagnosis may be necessary in order to arrive at the correct solution of the problem.

There are atypical cases of coronary thrombosis where only extensive experience and the application of all available data will be necessary to prevent making erroneous diagnoses. In particular is this true in the occasional instance in which pain does not occur. Here there is apt to be sudden dyspnea and a feeling of weakness. In such cases the dyspnea will be found to be out of proportion to the other evidences of heart failure (cases 34 and 46). When such a condition is found, a low blood pressure, if it was known to be high in the past, together with other features like minor changes in the electrocardiograms would give one the proper clue.

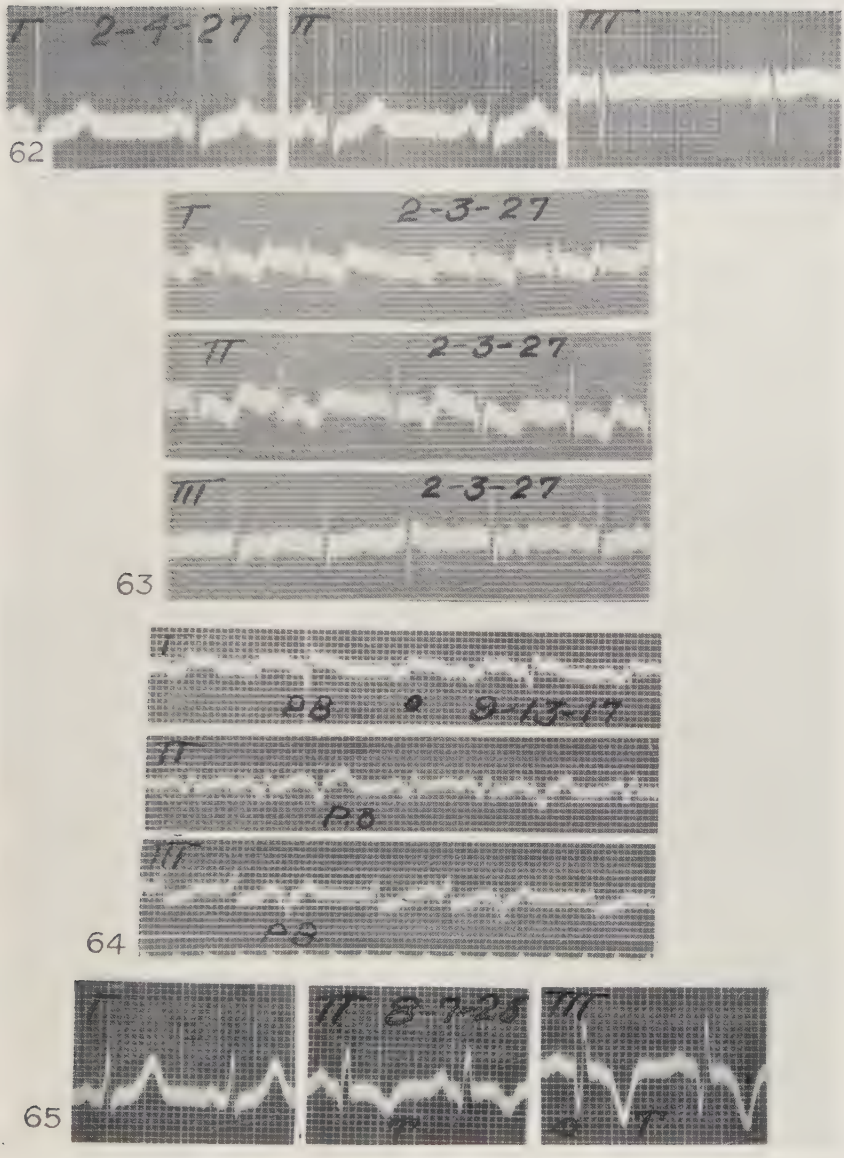
There remains a final group that is most difficult to recognize, namely, where the coronary vessels are slowly narrowing and infarction of the heart occurs without any any real acute episode to call attention to the condition (case 4). This generally occurs in patients that have progressive failure and are regarded as suffering from chronic myo-

FIG. 62. Case 113. Attack February 4, 1926. Note that the curves are essentially normal and give no indication of the attack of coronary thrombosis one year before. Patient still has anginal attacks.

FIG. 63. Case 135. Attack January 27, 1927. Note that auricular fibrillation is present. T 2 has the suggestive rounded and dipped form. Died February 7, 1927. Autopsy showed fresh infarction of left ventricle.

FIG. 64. Case 4. Probable date of attack September 3, 1917. Note the low amplitude of the ventricular complex. Every third cycle is a premature ventricular beat (P.B.). Died September 13, 1917. Autopsy showed typical thrombosis of left coronary artery and acute infarction of the ventricle.

FIG. 65. Case 115. Attack July 3, 1925. Note the sharp V-shaped inversion of T 3 and the prominent Q 3. Such curves are frequent a few weeks after the attack. Patient recovered very satisfactorily and died suddenly May, 1927.


I 2-4-27
II
III
62
I 2-3-27
II 2-3-27
III 2-3-27
63
I
PB 9-13-17
II
PB
III
PB
64
I
II 8-7-23
III
65

FIGS. 62–65

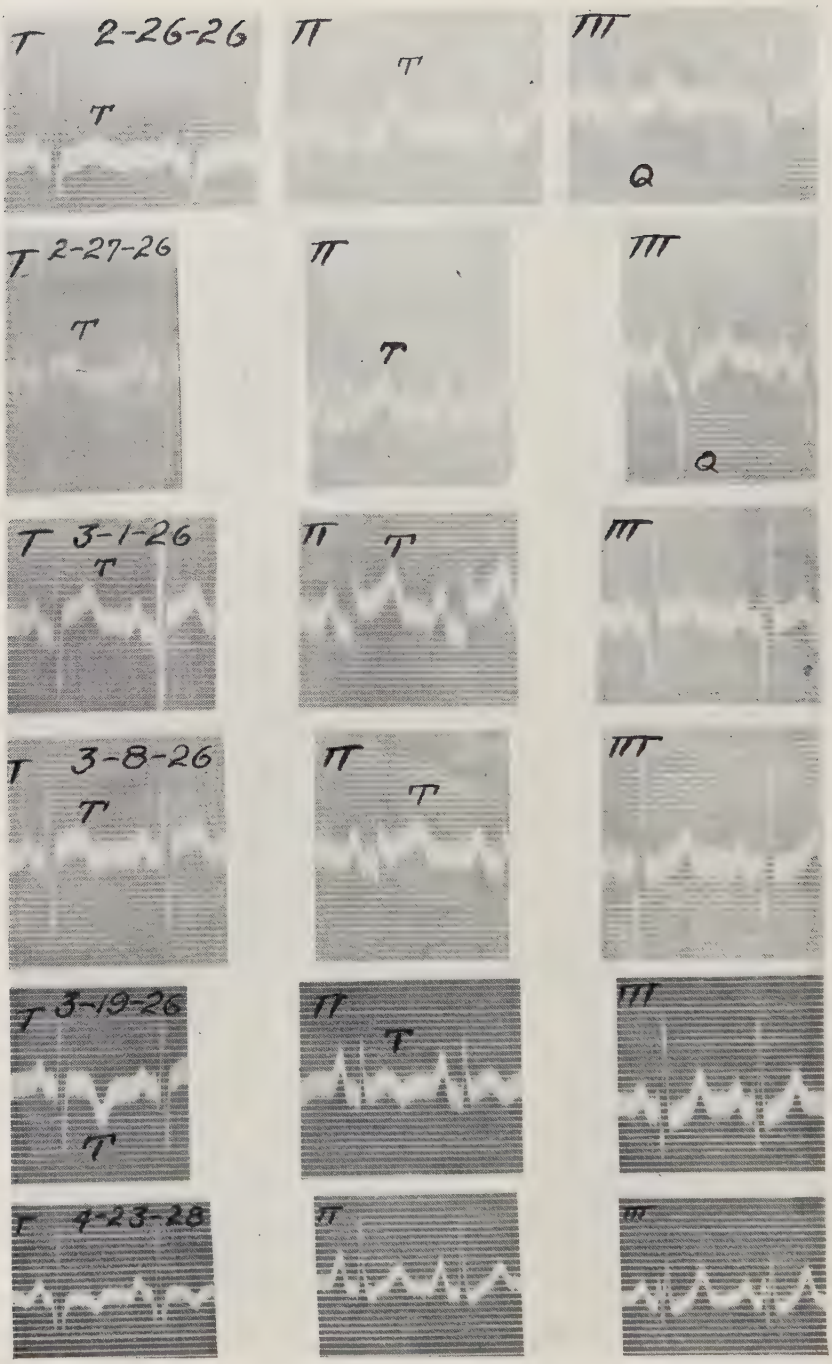


Fig. 66. Case 61. Attack February 26, 1926. The high take off of T 2 does not occur in the first tracing, but is most definite three days after the attack. Q 3 is also noteworthy. Patient recovered but two years later still has anginal attacks.

carditis. Even in this group it is not unlikely that in the future a more painstaking appraisal of all of the features of coronary disease will enable us more properly to anticipate these pathological changes.

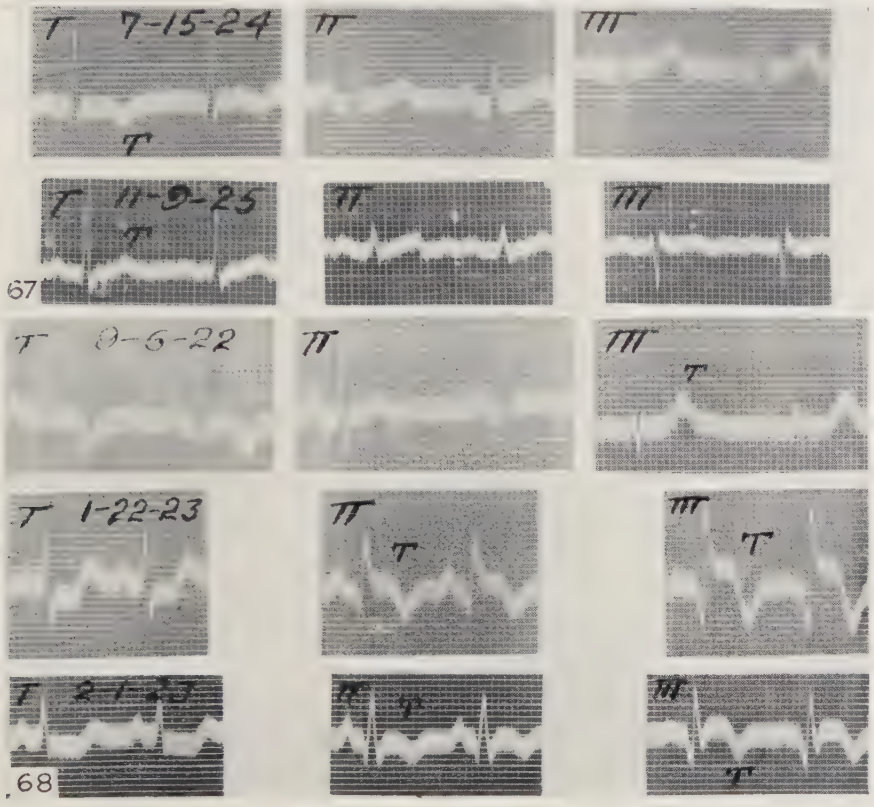


Fig. 67. Case 119. Attack June 11, 1924. T 1 is very slightly dipped in the first set of curves. The following year the electrocardiograms are essentially normal. Patient has done well for 3½ years.

Fig. 68. Case 19. First attack August 26, 1922, and second attack January 14, 1923. Note the decided change in the T waves after second attack. The typical high take off of T 3 and the peculiar Q 3 are present. Died February 3, 1923.

V. PROGNOSIS

There are few diseases in which the prognosis in any individual case is more difficult to predict than in coronary thrombosis. The data

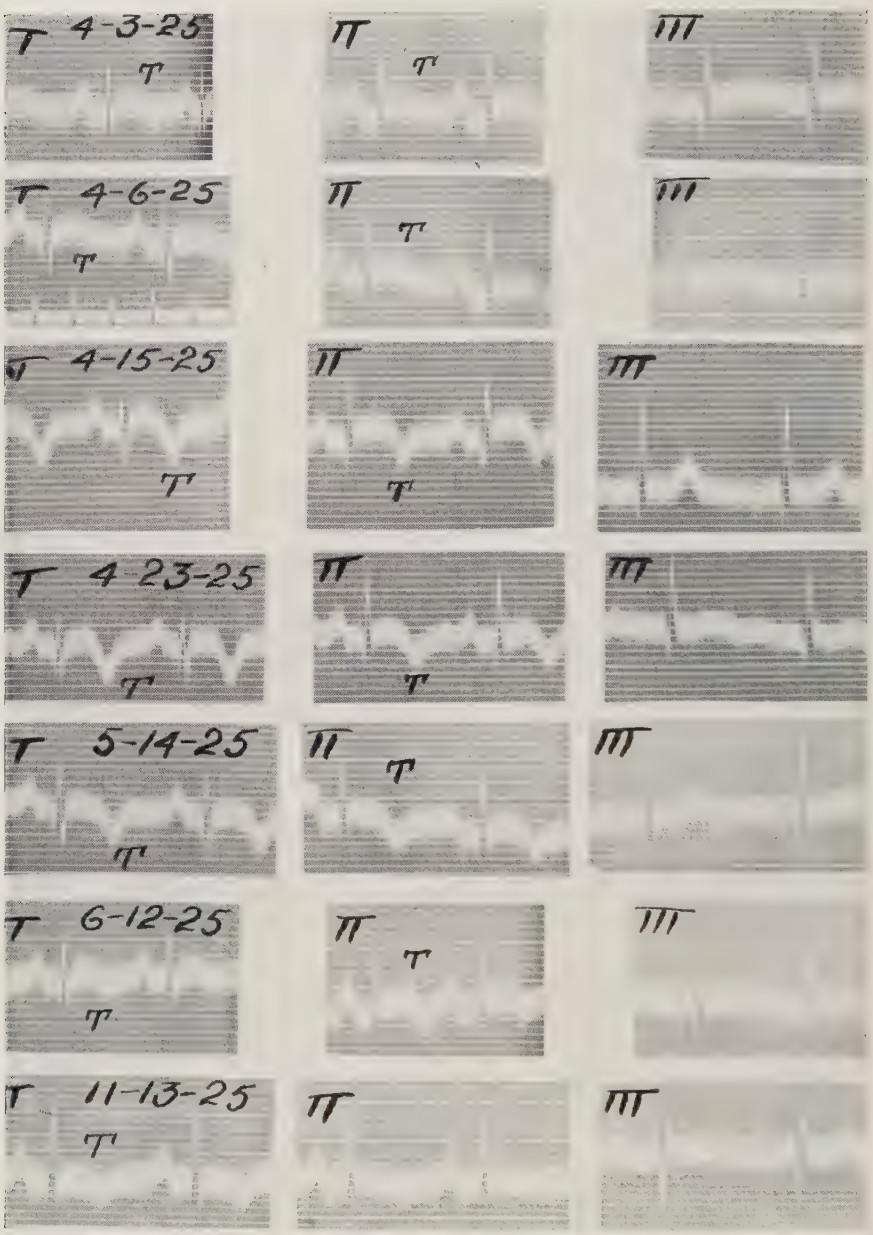


FIG. 69. Case 52. Attack April 1, 1925. Note the definite change in the form of the T waves. Patient recovered and has been quite well for 2½ years.

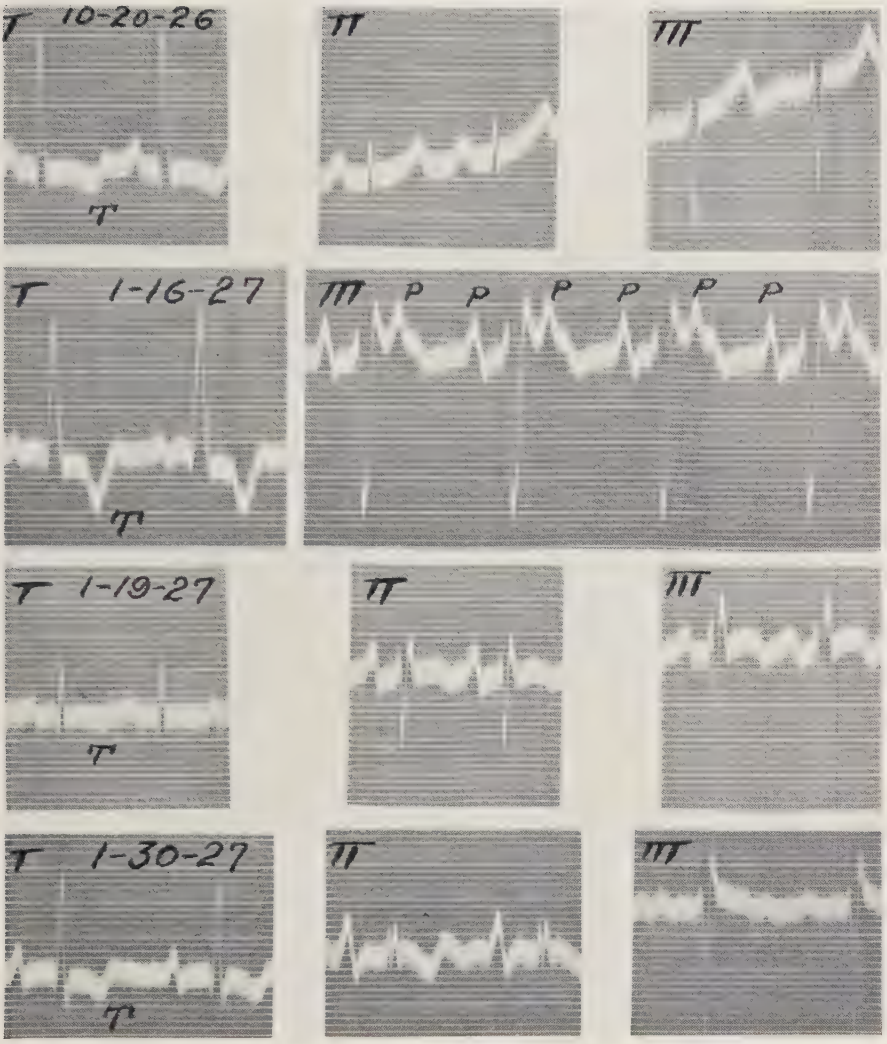


FIG. 70. Case 137. Attack January 10, 1927. First tracings taken after attack January 16, 1927, show 2 to 1 heart block. Patient died August 18, 1927.

here assembled afford sufficient opportunity to make generalities, but it is striking that there is hardly any specific criterion that is decisive or indicative of probable recovery or of the reverse. A patient may

seem to have had a mild attack and be progressing most satisfactorily, having no complaints and showing nothing remarkable on examination, and then die suddenly on the fifth to seventh day after the attack (case 1). The reverse is true, namely that after a very violent attack with serious complication, recovery can take place (cases 39, 40 and 133). For this reason the prognosis in all cases must be guarded until a few weeks have elapsed, and contrariwise, hope should be held out and every effort in the way of treatment should be carried out in the face of apparently desperate circumstances.

The general immediate mortality of coronary thrombosis is approximately 53 per cent, for of the 143 cases in which the outcome was known, 76 died and 67 recovered. How near this figure actually is to the truth is questionable, for the cases that die instantly are not seen by the physician and very likely many milder cases occur that we do not see, but these two factors probably counterbalance each other. One might fairly consider that a patient has an even chance to survive an attack of coronary thrombosis. After recovery has taken place the average duration of life in this series was about 24 months, but this includes 42 individuals who are still living. Another calculation is the length of life of those who have died after recovery from the immediate effect of the attack. Of 19 such patients the average length of life was 22.6 months. One can merely predict at present that when the final outcome of the entire series is known, the average length of life will probably be about three years with extreme variation of from a few months to ten or more years.

The factor of age is of some importance in the prognosis as far as immediate recovery is concerned. The average age of those who recovered was 54.7 years, of those who died was 61.0 years, and of the

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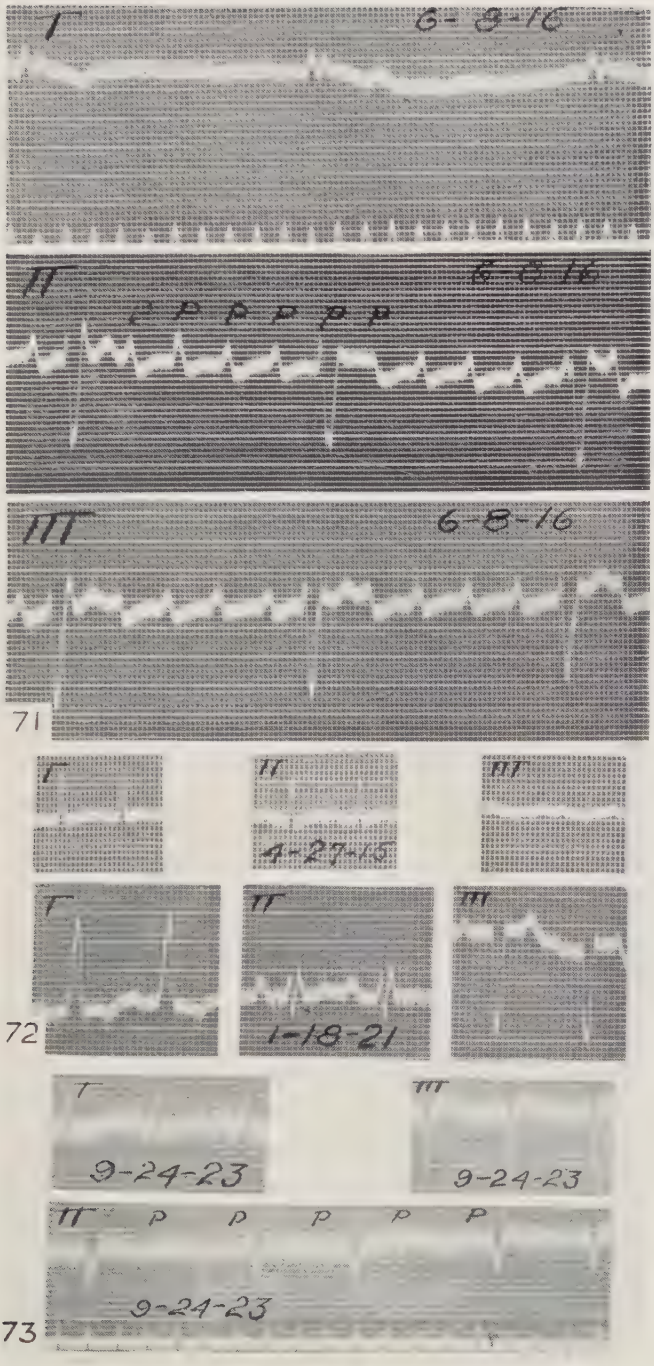
Fig. 71. Case 3. Attack June 6, 1916. Complete heart block is present. Auricular rate 143, ventricular 29. Died June 8, 1916. Autopsy showed left coronary artery thrombosis and fresh infarction of the ventricle. This was the first case in this series correctly diagnosed antemortem.

Fig. 72. Case 2. Date of attack in doubt, may have been January 18, 1921. The only significant change after the attack is the spread in the Q R S complexes. Died January 18, 1921. Autopsy showed infarction of the left ventricle.

Fig. 73. Case 21. Probable date of attack August 23, 1923. Partial heart block is present. Died September 26, 1923. Autopsy showed infarction of the apex of the left and right ventricles.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6-9-16
II
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III
6-8-16
71
I
II
4-27-16
III
I
II
1-18-21
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72
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9-24-23
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9-24-23
II P P P P P
9-24-23
73

FIGS. 71–73

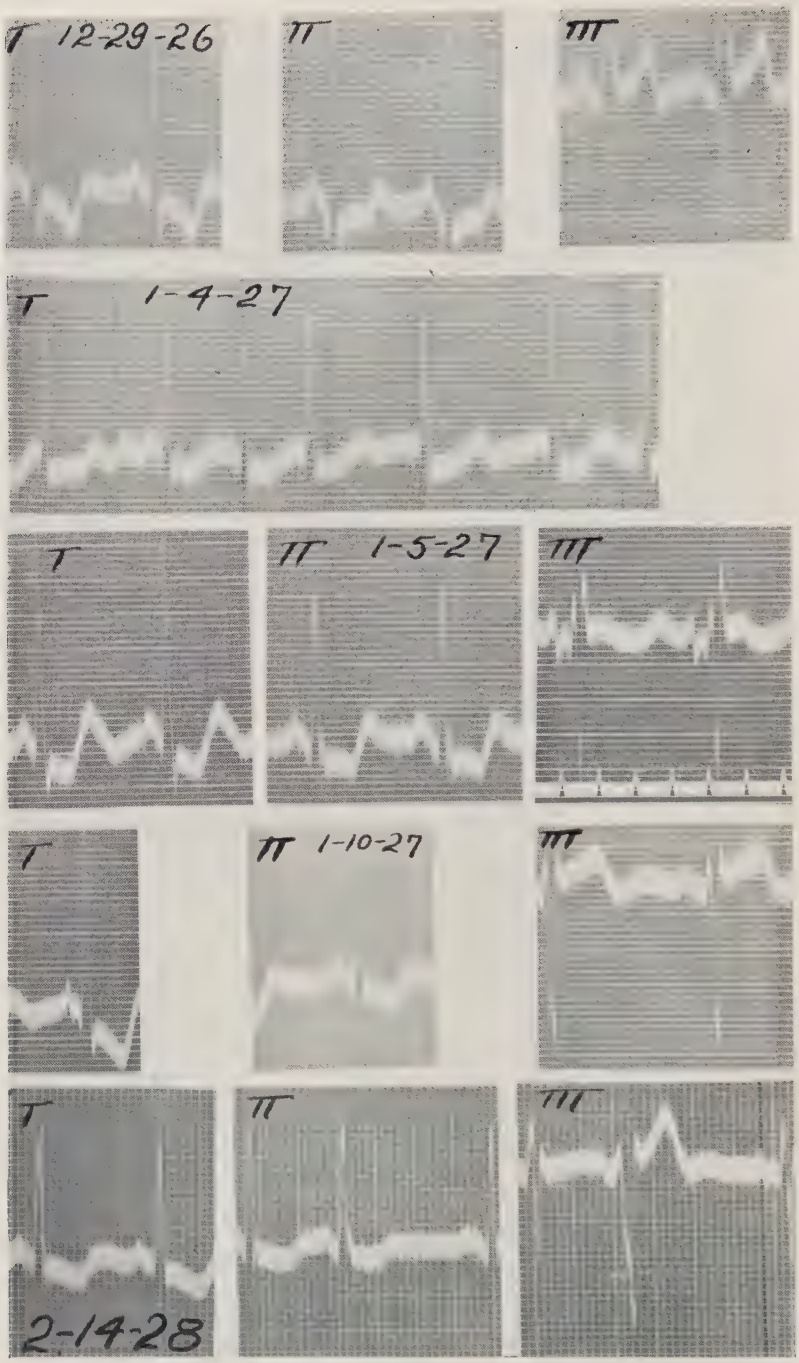


FIG. 74. Case 134. Attack December 27, 1926. Transient auricular fibrillation is shown on January 4, 1927. Patient recovered and has done well for one year.

entire group 57.8 years. This would indicate that the younger are a little more apt to recover. It is also true that having recovered from the attack, the younger are more apt to continue in good health for a longer time. There is a small group of patients of the age of about 50 who, having recovered, continue to do well and remain active for more than three years. It is essentially this group of patients that lends hope to the problem of therapy, because we know that it is possible for one to go through even a terrific agonizing attack of coronary thrombosis and make a recovery that can be considered to be complete in the sense that complete restoration of function results and continues for years. There were in this series 11 patients who lived three years or more after the attack, of whom four died and the other seven are still living. Their average age was 52.3 years, and the average length of time they lived was 51.1 months. Six patients lived four years or more, of whom five are still living, and two are alive more than five years after the attack. The above data do not include a small number of patients whose subsequent histories could not be traced.

The matter of sex does not alter the prognosis. The proportion of males to females among the fatal and recovered cases was about the same, i.e., approximately four to one. It is peculiar, however, that among the eleven who survived for three or more years there were no females. Although the group is quite small, it leads one to think that after recovery has occurred the females are not apt to remain in good health for as long a time as the males.

There is no evidence from this study that a previous or concomitant occurrence of glycosuria alters the age at which coronary thrombosis occurs or the prognosis. There were 34 such patients, 22 males and 12 females. The average age was 58.1 years which is approximately that of the entire series, and the immediate mortality was 58.8 per cent. The same is true of the prognosis in relation to syphilis, although this impression rests on very little data. There were only three cases out of 89 that had a positive Wassermann reaction, and one other had a definite history of a primary lesion. Considering these four as luetic, the average age was 52 years. One died aged 72 with a ruptured heart. Another died aged 47 and autopsy confirmed the diagnosis of coronary thrombosis and syphilitic aortitis. A third aged 36 recovered, and has been in normal health for over three years since the attack, and the

last one, 52 years old, recovered and has been well now for over five months. It is interesting that the youngest one of the entire series was a luetic aged 36 and he has had a splendid recovery.[3]

Likewise previous hypertension did not affect the age at which coronary thrombosis occurred or the mortality. There were 58 cases in whom it was known that hypertension existed. The average reading in this group was systolic 190.6 mm. and diastolic 109.9 mm. The average age of these 58 patients was 58.5 years, and the mortality was exactly 50 per cent. This corresponds very closely with the entire 145 cases and quite definitely proves that hypertension does not affect the prognosis. The development of pericarditis only slightly altered the outcome. Of 20 such cases, 13 died and 7 recovered. The average age here was 59.3 years. It would seem that the prognosis was a little more serious for cases developing a pericardial friction rub than the general average.

The relation of disturbances in rhythm of the heart and prognosis is quite interesting. The two most common irregularities were extrasystoles and auricular fibrillation. There were 35 of the former, of which 19 died and 16 recovered; and 34 of the latter, of which 18 died and 16 recovered. The average age of those who developed auricular fibrillation was 59.1 years. These figures are close enough to the general

[3] A case was recently seen by one of us, not included in this series, in which a severe typical attack of coronary thrombosis occurred in a man 24 years old. There was no evidence of syphilis and the patient recovered.

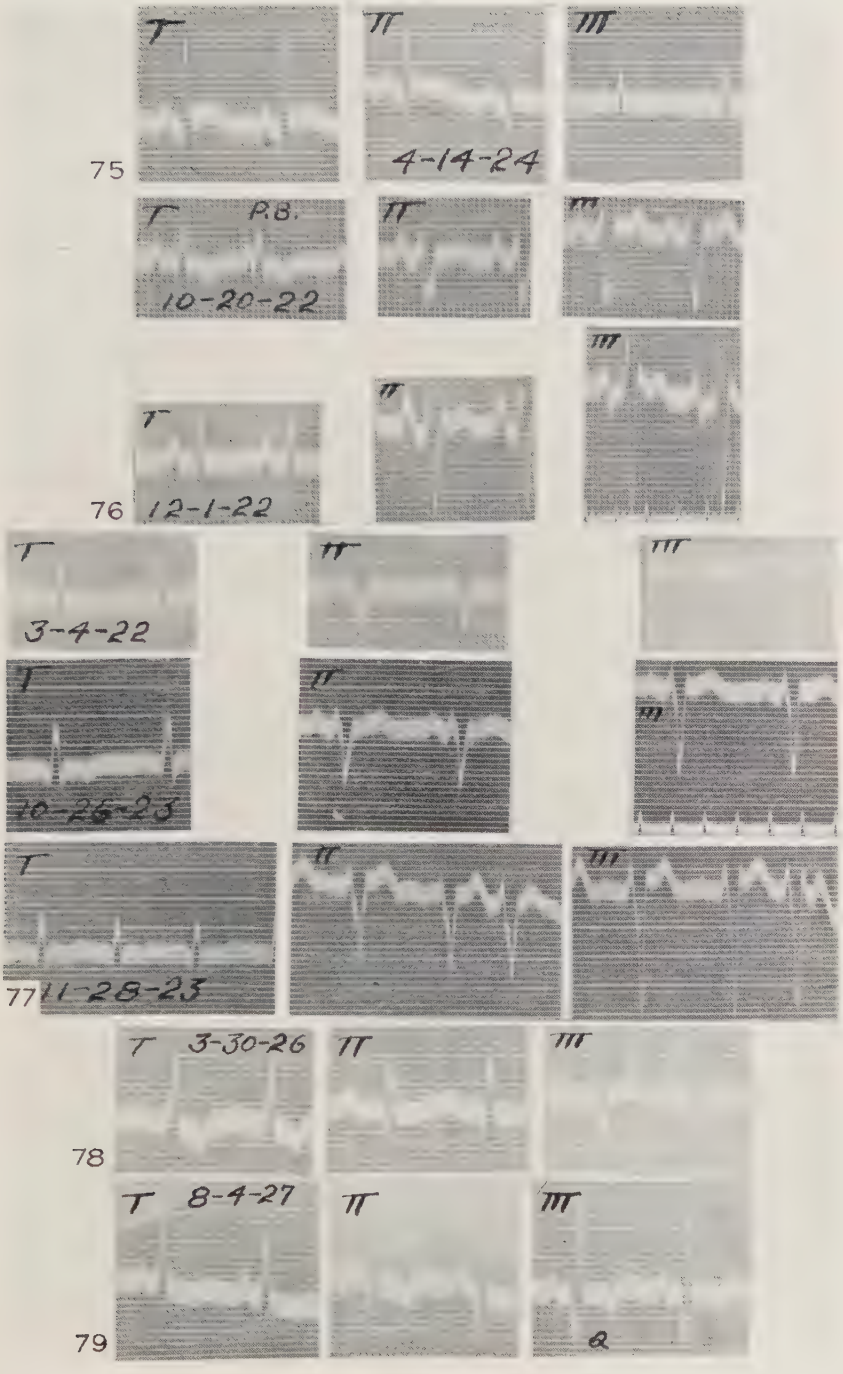
FIG. 75. Case 26. Attack April 9, 1924. Note the high take off of T 1 and T 2. Patient died April 23, 1924. Autopsy showed thrombosis of the left coronary artery.

FIG. 76. Case 50. Probable date of attack September 19, 1922. The first tracings show slight notching of the Q R S waves, which disappeared, and in lead I there is a premature beat, probably of nodal origin (P.B.). Died December 19, 1922. Autopsy showed occlusion of left coronary artery and aneurysm of the left ventricle.

FIG. 77. Case 22. Attack October 18, 1923. Transient auricular fibrillation occurred. Died December 3, 1923. Autopsy showed thrombosis of the left coronary artery.

FIG. 78. Case 64. Date of attack could not be determined. Note the notching of the Q R S waves. Died May 10, 1926. Autopsy showed both an old and recent infarct of the ventricle.

FIG. 79. Case 144. Probable date of attack July 25, 1927. Note the presence of Q 3 and the rounded and dipped T 3. Died August 7, 1927. Autopsy showed a fresh infarct of the left ventricle.


75
I
II
4-14-24
III
I P.B.
10-20-22
II
III
76
I
12-1-22
II
III
I
3-4-22
II
III
I
10-26-23
II
III
77
I
11-28-23
II
III
78
I 3-30-26
II
III
79
I 8-4-27
II
III
Q

FIGS. 75–79

average of the whole group to show quite clearly that these two arhythmias do not affect the mortality. The same in general is true of partial heart block, for of the 10 who showed this change, six died and four recovered. The two patients who had complete heart block both died, although a case of this type has come to our attention that recovered satisfactorily. There remains the group of five cases who developed paroxysmal ventricular tachycardia, of whom four died and one recovered. These last two types of arhythmia (heart block and ventricular tachycardia) were seen too infrequently to enable one to make generalizations, but there is some reason to regard them as indicating a graver prognosis, inasmuch as the one probably results from an involvement of the interventricular septum where the conduction tissue is found and the other indicates a degree of ventricular irritability that is closely related to ventricular fibrillation.

There are many other features that are measured less accurately which may have a bearing on the likelihood of recovery from an attack of coronary thrombosis. The severity and duration of the pain is difficult to estimate accurately, but the impression obtained from observation of many patients during the acute stages is that the character of the pain served as a poor guide to the outcome. There were quite a few fatal instances in which the pain was comparatively mild or of short duration, and vice versa, some in whom the pain was beyond description recovered satisfactorily. The degree of collapse or prostration is more helpful in estimating the prognosis. Unconsciousness

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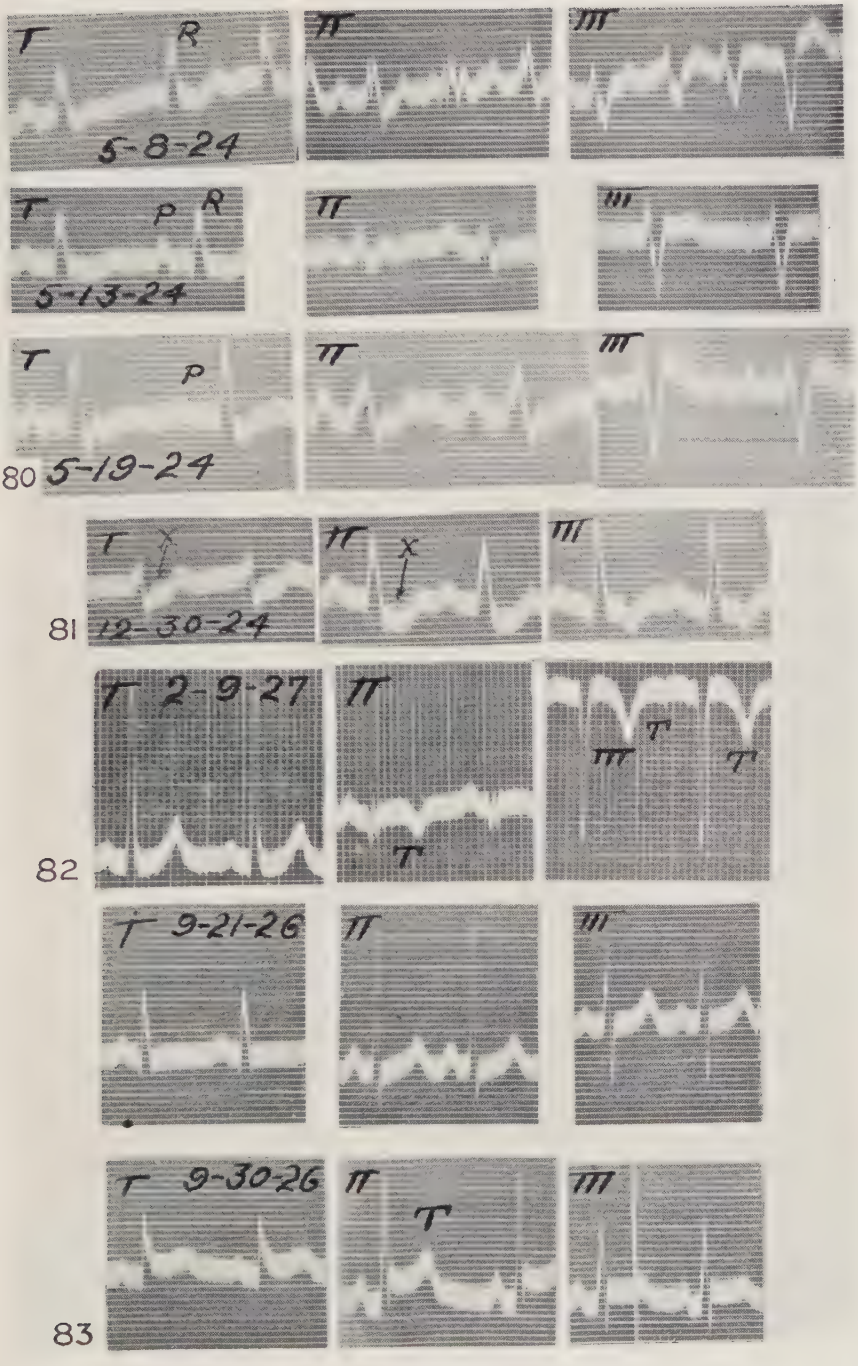
FIG. 80. Case 27. Attack May 1, 1924. The first set shows transient auricular fibrillation. Patient recovered satisfactorily, but died suddenly four months later.

FIG. 81. Case 37. Attack December 28, 1924. Curves are not remarkable except for slight spread of the Q R S waves. There is a minute wave marked X at the beginning of the T waves that has been thought to be significant. Died December 30, 1924. Autopsy showed infarct of posterior wall of the left ventricle.

FIG. 82. Case 126. Attack January 11, 1927. Note the sharp inversion of T 3 and the rounded form of T 2. Patient recovered and has done very well for one year.

FIG. 83. Tracings taken September 21, 1926, and September 30, 1926, from a case of chronic glomerular nephritis with uraemia. The 'phthalein output was 0 and the blood urea nitrogen was 217 mgm. per 100 cc. (September 28, 1926). Had a pericarditis September 23, 1926. Note the high take off of the T waves in all leads, especially in lead 2. The general form of the T wave is unlike those found in coronary thrombosis. Autopsy showed no coronary disease or infarction of the heart There was an acute fibrinous pericarditis.


I
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5-8-24
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X
81 12-30-24
II
III
I 2-9-27
82
II
T
III
T
T
I 9-21-26
II
III
I 9-30-26
83
II
T
III

FIGS. 80–83

at any time during the illness is rarely recovered from unless it is merely momentary. When the blood pressure is below 85 mm. the condition should be regarded as most grave. Mental changes like delirium or irrational agitation have a similar significance. Although the degree and duration of the fever and leucocytosis probably indicate the extent of infarction of the ventricles and in that sense reflect the amount of involvement of the heart, it is surprising how often recovery takes place after several days or more of such a reaction. While in general it is true that an attack that seems mild, as indicated by the symptoms of circulatory failure (i.e., dyspnea, cyanosis, oedema of the lungs, rapidity of the pulse, the level of the blood pressure and the appearance of the patient), will have a better prognosis than when more severe findings exist, there are numerous exceptions to this rule.

There remains one final consideration to take up that might aid in determining the prognosis, namely, electrocardiography. Here, again, it will be seen that the various changes that are observed do not materially affect the immediate outcome. There were 14 instances where the electrocardiograms were considered to be of small amplitude (i.e., of low electrical potential). Of these, seven died and seven recovered. The characteristic changes in the form of the T wave, or to be more accurate, of the R-T interval, were much more frequent. They occurred with equal frequency in leads 1 and 3, and somewhat less often in lead 2. The most characteristic type of change was a high take-off of the T wave from the limb of the R wave. Other changes that were considered to be due to coronary thrombosis, but less pathognomonic, were the rounded form of the R-T interval, with a peculiar dip to it, and the sharply inverted V shaped T wave. The above changes were observed 25 times in lead 1 and 26 times in lead 3. The data are not sufficient to draw any generalizations, but it would seem that when they occur in lead 1 the outlook is certainly not any more serious than in the average case, and possibly it may even be more hopeful, for the proportion of recoveries to fatalities was about two to one. This was also in general true when the T wave changes occurred in lead 3. A final consideration is the peculiar appearance of prominent Q waves in lead 3. These were sometimes transient and at other times persistent. There were 14 such instances, and of these 10 recovered and four died. This sign in so far as the present series indi-

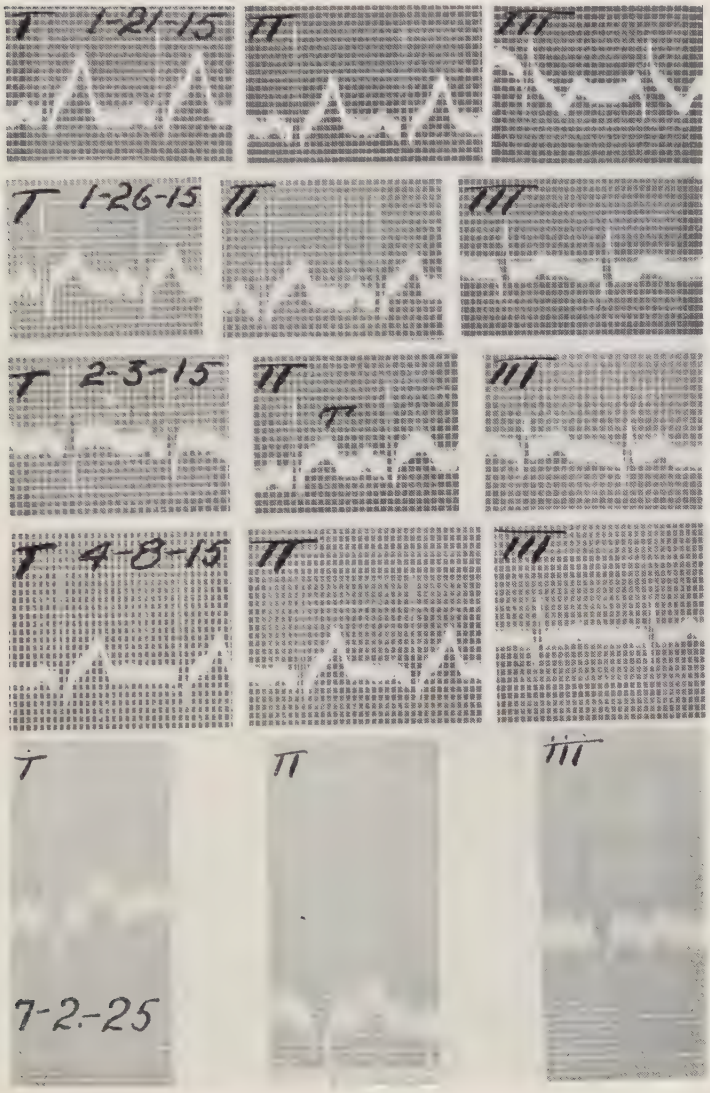

FIG. 84. The first four sets of electrocardiograms were taken during a course of rheumatic fever and acute pericarditis. Note the changes in the form of the T waves. There is a high take off of T 3 which does not become rounded or dipped. These curves need be distinguished from those found in coronary disease. This patient is essentially well 12 years later.

cates, would suggest a more hopeful prognosis than the general average. The significance of other changes like bundle branch block, defective interventricular conduction, etc., could not be ascertained, as they occurred too infrequently.

VI. THE TREATMENT OF CORONARY THROMBOSIS

It would be presumptuous at the present stage of our knowledge to formulate fixed principles for the treatment of this condition, because it is only in recent years that it has been recognized clinically with any regularity. For this reason, accurate observations extending over many years enabling one to compare the results of one method of therapy with another are lacking. A further difficulty is the abruptness of the onset of symptoms, the rapidity of the progress of the disease, and the suddenness of the complications that may arise. Our ideas of treatment, although partly based on experience, which in all practice may be fallacious, but particularly so in this connection, will need to rest in a measure on a theoretical basis, having in mind the pathological physiology of the underlying process and the gross anatomical changes that are being combated. In some matters it will be seen that we have knowledge, in others only opinion or judgment, but at any event there are certain principles that will help in formulating the proper treatment for this condition.

At the outset, the cardinal symptom for which relief should be afforded if possible is the agonizing pain in the chest. For this, nitroglycerin, which had formerly helped the patient, will generally be useless. Large doses of morphine should be given subcutaneously. The first dose administered should not be less than $\frac{1}{4}$ grain, and it is useless to give it by mouth. In many cases it may be anticipated that more than this amount will be necessary, so that we have frequently given an initial dose of one half grain. The morphine should be repeated as freely and as frequently as necessary. Often a whole grain can be given in a few hours. It must not be inferred that such large doses are always used, as frequently one or two injections of one quarter grain afford relief. When this is obtained, the acute pain subsides, and although a dull sense of oppression in the chest may remain, the patient is apt to fall asleep. Should the pain return, or even in the absence of pain, if there is restlessness and wakefulness, and the respirations

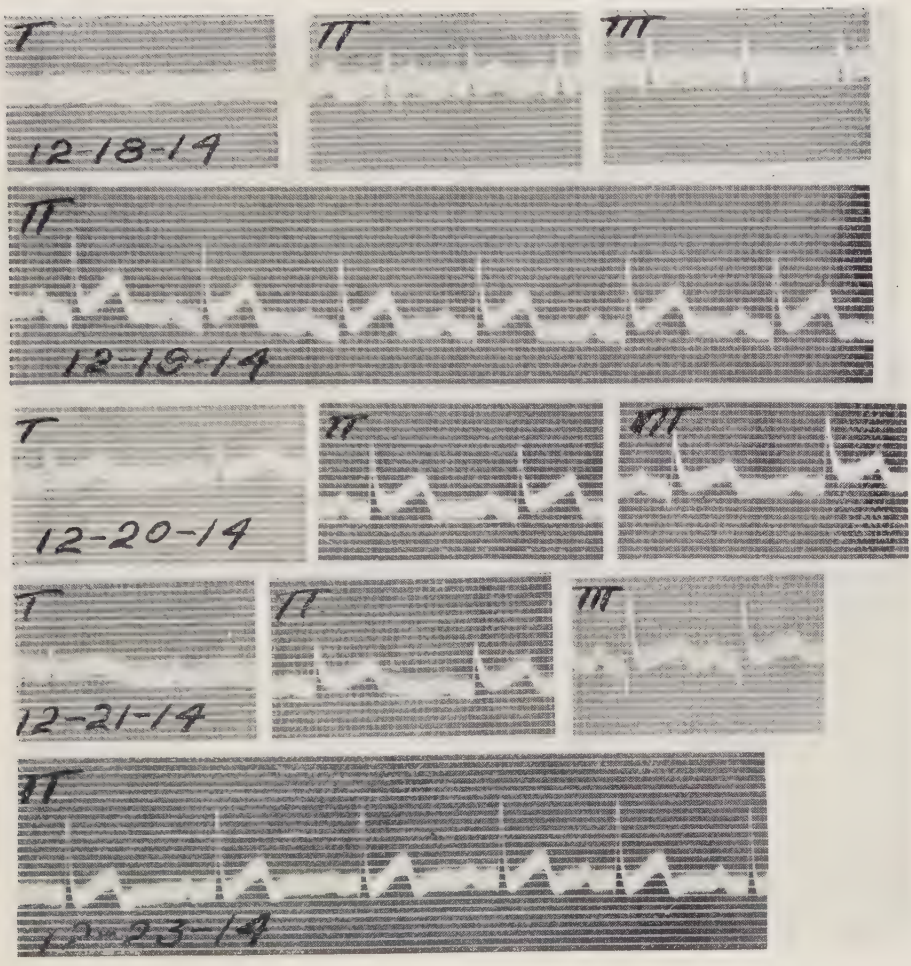

FIG. 85. Tracings taken during the course of acute lobar pneumonia. All but the first set were after the crisis. Patient recovered completely. Note the high take off of the T waves. Such curves might possibly be confused with those found in coronary disease.

have not been particularly depressed by the morphine, it is desirable to give a further hypodermic injection to assure rest during the following hours.

In a large number of instances, no other medication is necessary. If the patient is in extreme agony, and the morphine proves to be of no avail, it is not inadvisable to administer light ether anaesthesia. Recently a case was observed in which this was done in order that the patient who suffered an attack in the street might be brought home (case 116). It produced the desired result without any mishap, and, after a long convalescence, he eventually recovered. It seems advisable to abbreviate as much as possible the duration of the extreme pain, for apart from the relief of suffering that we thereby obtain, the general appearance of the patient is apt to be better as the agony disappears.

With the onset of the attack there quickly develops a state of shock. The patient has a cold sweat, and there is the ashen gray appearance that is quite characteristic. The immediate question that comes up is the matter of stimulation. It is our belief that if the peripheral pressure is sufficient to maintain even a comparatively feeble circulation, stimulation is to be avoided. There are instances where the pulse is absolutely or almost entirely imperceptible. Here the intraveneous or intramuscular administration of large doses of caffeine sodium benzoate (0.5 to 1.0 gram), strophanthin, or adrenalin intramuscularly may be carried out. But in most cases, although the patient is in shock, the blood pressure will still be sufficiently high. If the blood pressure is 100 mm. or over, it is our belief that the relief of pain is all that is needed and that one should avoid stimulation if possible. The body, however, should be kept warm by the suitable use of blankets and heating appliances.

A consideration of what is taking place within the heart during the first hours and days of the attack is necessary to clarify and rationalize the treatment. At the outset a coronary vessel is partially or completely occluded with the resultant symptoms of pain and collapse. That portion of the ventricles that was supplied by that vessel begins to undergo infarction. Although the process probably begins directly, the important secondary changes like softening, rupture, local mural thrombus formation, and local aneurysmal formation take days to develop. It is mainly with regard to the dislodgment of an embolus

from the ventricular thrombus and the rupture of the ventricle that stimulation of the heart is to be avoided. The more forcefully the heart contracts, the more likely it would seem that either of these two catastrophies might occur. It is logical, therefore, to welcome a sluggish contraction of the heart provided the circulation be sufficient to prevent local stagnation and thrombosis and marked anoxemia. Inasmuch as rupture of the heart or embolic phenomena are not apt to occur the first few hours or even the first day of the attack, the problem of stimulation is different at this time than it is several days later. Whereas it may be necessary and safe to stimulate at the onset, it is generally inadvisable after the first day or two.

As in all heart conditions, the possible use of digitalis must be be considered. We have in general entirely avoided the administration of digitalis. One reason for this is that it is undesirable to stimulate the heart. Secondly, not much is to be hoped for from digitalis for under circumstances that prevail during an acute attack, the heart is regular and its rate will be little if at all influenced by digitalis. Finally, digitalis may possibly make more irritable a ventricle that is already irritable as is shown by the occasional development of ventricular tachycardia. If the latter effect of digitalis is real the possibility of ventricular fibrillation and death would be greater in the digitalized than in the undigitalized patients. It is true, furthermore, that many of our most successful recoveries have taken place in those cases where no digitalis whatever was used.

The problem is quite different during the first hours. When the patient is in collapse and the pulse imperceptible, there is as yet no danger of rupture or emboli and vigorous stimulation seems logical. What is actually accomplished it is very difficult to appraise. Many things are often done in quick succession in the hope that one of them might prove helpful, and if the patient improves we are at a loss to know which one of the drugs, if any, was effective. There is some basis, however, for believing that caffeine, adrenalin and intravenous strophanthin may be of help. The caffeine could be acting as a stimulus to the respiratory center, and in many instances there is marked dyspnea; the strophanthin or adrenalin might be exerting a supportive influence on the circulation. During these early days there are instances where oedema of the lungs, respiratory distress and cyanosis are

prominent. Under such circumstances, the inhalation of oxygen, preferably administered by means of an oxygen tent, may be of benefit merely as an aid in obtaining a better aeration of the blood. The value of oxygen cannot be great, but nevertheless it may make the patient more comfortable and ameliorate the symptoms of dyspnea and cyanosis, as it does in pneumonia.

If there develops evidence of congestive heart failure, such as pitting oedema of the legs, engorgement of the liver, hydrothorax and the like, which is most apt to happen after the first two weeks and after the danger period of rupture of the heart and embolic dislodgment, it is best to digitalize the patient just as one does under similar circumstances when any patient has general circulatory insufficiency. This is particularly true if persistent auricular fibrillation occurs as occasionally happens. In other words, following an attack of coronary thrombosis, the problem of ordinary heart failure may need to be met with, and all the measures ordinarily employed, including phlebotomy, digitalis and diuretics are then to be used.

The treatment of coronary thrombosis is mostly concerned with the care of the complications that arise. One of the more uncommon occurrences is the development of complete heart block and attacks of syncope. For this particular condition the intramuscular injection of adrenalin is distinctly indicated, inasmuch as such attacks are apt to last only a short time and are quite beneficially influenced by this drug. Should recurrent attacks of Adams-Stokes syncope develop, barium chloride may be tried according to the methods recently described (68).

There is one unusual complication of coronary thrombosis, which although rare is quite important because if unrecognized or improperly treated may in itself prove fatal, whereas under proper medication recovery can take place. This is the inception of ventricular tachycardia. Any sudden rapid heart rate, if maintained over a long period of time, will enfeeble the already damaged circulation to a disastrous extent. The most common type of such a paroxysm of rapid heart action is an attack of transient auricular fibrillation which generally lasts only several hours, and is not particularly disturbing. A rarer type of disturbance is paroxysmal ventricular tachycardia, which again may be transient, only lasting a few hours. At times, however, this

may continue for days and then becomes most serious. The clinical bed-side recognition of this condition has been considered in the past either very difficult or impossible, requiring accurate interpretation of electrocardiograms. Recently, however, several clinical features that can be detected at the bed side have impressed us so that probable diagnoses have been made which were proved to be correct by subsequent electrocardiograms. The criteria that enable one to make this bed-side diagnosis were taken up in detail above under the discussion of the arrhythmias and, therefore, will not be gone into here.

When the complication of ventricular tachycardia develops the proper treatment is quinidine. There is no other drug that is known to have any beneficial effect on it. Digitalis has proved to be of no value, and there is some reason to feel that it may even tend to perpetuate it. Scott (69) first called attention to the specific beneficial effect of quinidine on ventricular tachycardia, and we have had similar results (64). A very recent experience illustrated most dramatically the great importance of the proper use of quinidine in this condition. A man of 58 had had a terrific attack of coronary thrombosis and during the third week suddenly developed a heart rate of about 200, uninfluenced by vagal pressure. The rhythm was quite regular, but slight pauses were definitely detected, and there was a marked pulse deficit. The intensity of the heart sounds varied from time to time, and the bed side diagnosis of ventricular tachycardia was made, which was confirmed by electrocardiograms. The patient's condition quickly grew worse. Increasing doses of quinidine sulphate were given without any noticeable effect, until the single dose of 1.0 gram was reached. At this point it was noted that the occasional pauses were longer and more frequent so that the heart rate fell to about 175. The electrocardiogram showed that whereas most of the beats were ventricular in origin, occasional normal supraventricular beats were appearing (fig. 61). The patient's condition was quite low, the pusle was imperceptible, and the only hope lay in the possibility of breaking that rapid ventricular rate. He was therefore given 1.5 grams of quinidine sulphate five times a day, and the normal mechanism was established, the heart rate falling to about 100. The tachycardia had lasted 72 hours. For a day or so after this, on omitting the drug, the tachycardia reappeared. Quinidine was again given and the heart rate

returned to normal. After several days the drug was omitted entirely, and this time the rhythm remained normal. This patient recovered satisfactorily despite the fact that during the most critical times the prognosis seemed absolutely hopeless. One is warranted here in saying that the extreme doses of quinidine were probably life saving in this case. Quinidine sulphate, however, must be used with care and intelligence, for it is a double edge sword; it can kill as well as cure.

Apart from medication there is one procedure that should from a theoretical point of view add distinctly to our therapeutic agents, and that is the administration of oxygen. Cyanosis and oedema of the lungs are common features in acute coronary thrombosis. The enfeebled circulation with its secondary changes in the lungs must produce a distinct anoxemia or oxygen want. It would seem that the administration of oxygen in high concentration should prove helpful. We used the oxygen tent in the treatment of one of our cases and here the element of cyanosis was quite distinctly and rapidly improved, although the patient died with a ruptured ventricle some days later. Despite this single fatal outcome, there is every reason to advise the use of oxygen when it can be administered without particularly disturbing the patient.

There are other less impressive but none the less important points in the treatment of coronary thrombosis that deserve mention. Good nursing care is most essential. The patient's mind and body should be put at rest in the best possible manner. Visitors should be entirely avoided or at least restricted to one or two individuals. Long conversation or elaborate examination should be refrained from unless of direct value to the patient. During the first few days fluids should be given freely as the patient may become dessicated from the marked perspiration. The food is best confined to a milk diet and later other liquid and soft solid nourishment may be added. During the early days of the attack as a result of the large doses of morphine, the bowels are apt to become quite constipated. It has seemed best not to force any bowel movement for about 48 hours, and then to have the bowels move by enemata if necessary. A mild daily cathartic may then be given to prevent dessication of the stools and resultant straining that at times is very disturbing and exhausting. The nurse should be carefully instructed to do everything in her power to aid the patient in any

physical activity so that all possible movements such as feeding himself or lifting himself in bed are spared. It would be helpful if the nurse were trained to use a stethoscope, as they are in some hospitals, and follow carefully the rate and rhythm of the apex beat. In this way important changes in the heart mechanism would be detected sooner and more quickly treated. Finally, the patient should be urged to spend at least six weeks, and preferably eight weeks or more, absolutely in bed.

VII. PATHOLOGICAL CONSIDERATIONS

In the consideration of infarction of the heart from the point of view of morbid anatomy, the relationship of coronary disease to the infarction has long been understood. Weigert (70) in 1880 showed that infarction of the heart was analogous to infarction in other organs. Ziegler (71), in 1880, introduced the term of myomalacia cordis in referring to infarction of the heart. In the extensive literature of the pathology of heart disease, and particularly under that of angina pectoris and coronary sclerosis, many authors were responsible for the splendid descriptions of the lesions of infarctions of the heart and these papers provided additional cases which might be valuable in a statistical study. It is unnecessary to undertake a review of all such papers in a work of this kind. It seems quite logical that studies of the coronary circulation and attempts to produce cardiac infarction experimentally would follow these pathologic studies.

In 1881 Cohnheim and von Schultess-Rechberg (72) studied the pathologic anatomy in experimental coronary infarction in dogs and emphasized the conception of the coronary artery as an end artery. Porter (73, 74) in 1894 and 1896, was among the earlier workers to study experimental coronary infarction. In 1907, Hirsch and Spalteholtz (75) reported some experimental studies on dogs and showed that the coronaries anastomose with each other, in contradistinction to the view of Cohnheim and von Schultess-Rechberg. In more recent years the work of Gross (76), Wearn (50, 51) and others has demonstrated the remarkable anatomical features of the circulation of the heart. The experimental study of coronary infarction has been continued in recent years by Smith (77), Miller and Matthews (78) and Karsner and Dewyer (79). The last mentioned authors published

a splendid study of the gross and microscopic pathologic changes in experimental infarction in its various stages. The following is an account of the autopsy findings of our series, and it is presented mainly from the point of view of its aid in understanding the clinical problems involved in this disease.

The proper function of any tissue or organ is so dependent upon an adequate blood supply, that it is to be expected that any impairment in the circulation, whatever its nature, will be accompanied by characteristic pathologic findings and by more or less typical clinical features. Pathologists have long been familiar with the findings in infarction of the heart and early descriptions are found embodied in the extensive literature on coronary sclerosis and angina pectoris. Since not all patients suffering from coronary thrombosis succumb to the immediate insult of the attack, the pathologic study at once provides a greater interest than the mere recognition of the localized lesion at the necropsy table. The correlation of pathologic findings with the sequence of events enables us to anticipate not only the possible variations in the clinical picture, but the probable time relationship of such changes. An understanding of all possibilities in the pathologic process must lead to a more intelligent prognosis and rational therapy.

Post-mortem examination was performed on 46 cases of this series; of these 31 were males and 15 females. The ages represented in these cases were as follows: one case under 40; four cases from 40 to 49; 13 cases from 50 to 59; 19 cases from 60 to 69; eight cases from 70 to 79; and one case that was 80. The average age in the males was 61.3 years, the youngest being 39 and the oldest 80; the average age in the females was 61.8 years, the youngest being 41 and the oldest 76.

The striking and most characteristic lesion in all cases was the localized area of damaged heart muscle, the infarction itself. The most frequently encountered type was the recent infarction; this includes those cases showing acute and subacute pathologic changes, namely, extravasation of blood into the muscle tissue, necrosis and early repair by connective tissue proliferation. Here the classical pathologic picture was found. The line of demarcation between the infarcted and the uninvolved muscle was usually sharp, both in color and consistency. The muscle within the infarction appeared reddish

purple with a variable degree of yellowish mottling, and was softer in consistency than the uninvolved muscle. The deepness of the reddish purple coloring was dependent on the degree of extravasation of blood into the tissues while the mottling varied with the degree of necrosis. The softening was most marked when necrosis was greatest.

The appearance of the infarcted area depends quite definitely on the time that elapses between the attack and death. In this series of cases it was possible from the history and character of the pain to determine the time of onset in 24 cases. The time interval between the onset and death varied from 24 hours to several months. Twenty of these cases died within 30 days after the onset of the attack. During the first day the infarcted muscle would appear deeply red; this was largely due to extravasation of blood into the muscle. Some degree of necrosis of muscle fibres would be present also. The features due to extravasation of blood remained persistent for many days, but were particularly marked during the first three or four days. Necrosis of the heart muscle was a prominent feature from the beginning but from the fourth day to the end of the third week it was the predominating feature. This is a very satisfactory explanation of the occurence of rupture. All of the ruptures, with exception of one which occurred through an aneurysmal dilatation, occurred within two weeks after the onset of the attack. Six out of nine cases of rupture occurred in the interval of from five to fourteen days after the onset; this is the period during which necrosis is most marked and the muscle softest. Occasionally during this period some degree of liquefaction is grossly noticeable so that there is the appearance of multiple miliary abscesses in the heart wall in the infarcted area. Some necrosis may be present for several weeks.

Repair by connective tissue proliferation is demonstrable as early as the sixth or seventh day. Connective tissue replacement of damaged muscle, however, is not a striking feature until after the third week. It would seem that more than five weeks is required for cicatrization to develop adequately to prevent possible rupture (see case 16). Firm healing by vascularized scar tissue was observed eight weeks after the onset of the attack. So, even in this small group of cases, there are sufficient data to expect rupture rarely before the fifth day after the attack. It also follows that rupture is most likely to occur during the

second week after the attack and that healing sufficient to withstand the circulatory pressure may not take place until after the fifth week.

From a microscopic point of view, widely different elements in the same pathologic process may be demonstrated histologically within the same infarcted area. Edema and hemorrhage are likely to be the earliest manifestations of the acute insult. Shortly after this, necrosis of muscle fibres takes place and by this time leucocytes appear. Histolysis and liquefaction and leucocytic infiltration may become so extensive as to give the picture of abscess formation. All of this takes place during the first few hours and days and as indicated above, may be present to some degree for several weeks. Young connective tissue formation is demonstrable early and progresses fairly rapidly. Repair by connective tissue replacement and cicatrization apparently follows the same pathologic sequence as encountered elsewere in the body. The necrosis will be most pronounced in the central portion of the infarction, and usually the most marked connective tissue proliferation takes place when necrosis has been most active. Sections from different portions of the infarction may show all three of these pathologic proceses—hemorrhage, necrosis and connective tissue proliferation in varying degrees. In the same heart, muscle tissues outside as well as inside the infarcted area may show fatty degeneration which of course is rather early evidence of damage to the cells. It is logical to assume that interference with nutrition takes place to a greater or less degree long before the acute insult from complete blocking of the circulation actually occurs. As other evidence of previous damage to the area involved in the infarct, cicatrices are sometimes found within the recent infarction. These are likely to be small rather than large. The small scars may be seen as a part of the general process of a chronic fibrous myocarditis or in cases where diffuse coronary sclerosis has been present. If a single large scar is found in some portion of the recent infarction, recurrence or delayed extension within the same vascular distribution is suggested. In recent infarction the findings of subacute or chronic changes in close approximation to the acute changes suggests that not all of the injury followed an acute insult, but probably was gradual or even somewhat intermittent in its nature.

The most frequent location of the infarction was within the distribution of the anterior descending branch of the left coronary artery. The

boundaries of the portions of the heart supplied by the left coronary and the right coronary arteries are not sharp because their branches overlap and there are abundant anastomoses between the left and right coronary arteries in their capillary and precapillary distribution.

"The right coronary artery in the typical average heart supplies the entire right ventricle with the exception of the left third of the anterior wall. Besides this, its rami ventriculares sinistri supply the right half of the posterior wall of the left ventricle, and a small strip of the interventricular septum. The left coronary artery, on the other hand, supplies the whole remaining part of the left ventricle, the small left anterior portion of the right ventricle not supplied by the right coronary artery, and a small anterior strip of the interventricular septum. The areas of junction on the posterior surface of the left ventricle and on the anterior surface of the right ventricle, where these divisions meet, are supplied by both vessels. Thus, the intervening portion of the interventricular septum is supplied by branches from the ramus descendens posterior dexter and ramus descendens anterior sinister." (The Blood Supply to the Heart, Louis Gross, Paul B. Hoeber, N. Y., 1921, pp. 23, 24, 25 and 89.)

In this series of 46 cases the infraction was found within the distribution of the anterior descending branch of the left coronary in 39 cases (84.7 per cent); in the distribution of the circumflex branch of the left coronary in four cases (8.6 per cent); in the distribution of the right coronary artery in two cases (4.3 per cent). In the remaining case (case 37) the infarction involved a large portion of the posterior wall of the heart, the left ventricle more than the right, and also the left side of the interventricular septum. In this heart, the clacification of both the right and left coronaries was marked, and in the absence of definite thrombus it was difficult to ascribe the infarction to either vessel. The left seemed more at fault; at the division into the circumflex and anterior descending branches the calcification was so marked that the lumen in the circumflex was no larger than a small bristle. In the cases of blocking of the anterior descending branch of the left coronary the infarction most often occupied the anterior portion of the left ventricle in the region of the apex or slightly medial to the apex. In 14 of these 39 cases, the interventricular septum was involved to a variable degree. In three of the 39 cases (which also showed septal involvement) the anterior left portion of the right ventricle was also affected. When the

circumflex branch was obstructed, the infarction occupied the posterior portion of the left ventricle, usually fairly well toward the interventricular septum. However, in none of these cases was the septum involved. In one of the cases (case 5), where the right coronary was obstructed, both the right ventricle and the left ventricle, as well as the septum, were involved and the infarction was found largely on the diaphragmatic surface and extending toward the apex. In this case the blood pressure remained high (systolic 170 and diastolic 110) and there was no chest pain. In the other case of right coronary block (case 49) the infarction was in the right half of the posterior wall of the left ventricle and did not involve the septum. This last instance illustrates that infarction in the posterior wall of the left ventricle may arise from obstruction of the right coronary artery. In this case the blood pressure was low (systolic 115 and diastolic 70) and there was no chest pain with the attack. The fact that the infarction occurred in the left ventricle as a result of a thrombosis of the right coronary artery and that even rupture of the left ventricle took place in this case would make it seem questionable whether antemortem diagnoses can be made predicting which coronary artery is thrombosed.

The size of the infarction obviously must be of great importance. It would seem that the larger the infraction the more fatal the disease is likely to be. However, one can readily understand how the converse of this need not necessarily be true, as for example, a very small area deprived of its nutrition in a more vital portion of the heart structure might prove more quickly fatal than a much larger infarction at some other point. One can only guess about the size and location of the infraction in cases that recovered or did not come to autopsy. In this series of 46 cases the size of the infarcted area ranged from 2 to 8 cm. in greatest dimension, the average being from 3 to 5 cm. In the 24 cases in which the onset of the infarct seemed accurately timed, the size and location of the infarction could be found to bear no definite relationship to the length of life after the infarction occurred.

The area of infarction may or may not be extensive enough to involve either the pericardial or endocardial surface. It has been said that when the infarct is not extensive enough to involve the entire thickness of the cardiac wall, the area of damaged heart muscle is likely to be wider toward the pericardial surface than toward the endocardial

surface. The best evidence of endocardial or pericardial involvement is the presence of mural thrombosis or pericarditis, respectively. The ages of these lesions depend upon the age of the muscular lesion with which they are associated. In only three out of 46 cases were both the endocardial and pericardial surfaces undamaged over the area of infarction. In the remaining group of 43 cases mural thrombosis was much more common than pericarditis. Thirty-eight cases showed mural thrombosis over the area of infarction and 24 cases showed pericarditis grossly. All nine cases of rupture are included in this group with pericarditis, and here four cases had a very definite pericarditis, while in the remaining five the pericarditis could be recognized only because the clot was somewhat adherent over the area of infarction about the rupture. In the 38 cases with mural thrombosis there were 19 cases in which no pericarditis was present; in the 24 cases with pericarditis there were only four cases in which there was no mural thrombosis. In six out of the 38 cases in which mural thrombosis was present a thrombus was found in both the left and right ventricles; in all of these instances the area of infarction involved the interventricular septum.

The occurrence of infarction of the heart presupposes a basic lesion of such a character that in its development the lumen of the coronary artery was entirely or partially occluded, somewhere along its course. Arteriosclerosis of the coronary artery was almost always the causative basic lesion. In some instances the degree of coronary arteriosclerosis was found to be out of all proportion to the degree of arteriosclerosis elsewhere in the body. The localization of the sclerotic process in the heart itself was just as striking. A single small area of atheroma upon which a thrombus formed, was in many instances the sole arteriosclerotic lesion throughout the coronary vascular tree. In these cases little or marked arteriosclerosis might be found in other parts of the body. In contrast to the above pathologic changes there were a few cases in which the only vascular finding was a variable degree of arteriosclerosis present diffusely, particularly in the smaller coronary branches, without any demonstrable localized atheroma or thrombus to account for the infarction. In this last type the ordinary picture of diffuse coronary sclerosis and chronic fibrous myocarditis was more likely to be found in the heart muscle outside the infarction. Perhaps this

group provides many of the atypical cases, i.e., infarction without pain and infarction occurring in the course of heart failure. However, in some cases where there was no pain accompanying the infarction, a definite occlusion from thrombosis was found at necropsy (cases 6 and 46). Such vagaries of distribution still remain a mystery in the behavior of arteriosclerosis.

Syphilitic arterial disease seemed to play an important rôle in the production of infarction of the heart in a few instances. As a part of an extensive syphilitic aortitis the orifices of the coronaries may be partially or entirely occluded. When occlusion does occur the clinical picture is not different from that seen in cases of obstruction due to simple arteriosclerotic processes. The pathological changes of arteriosclerosis as well as that ordinarily ascribed to syphilis may be present in the same vessel. As brought out in the clinical discussion in this paper, the pathologic study would tend to show that syphilis alone is an infrequent cause of infarction of heart muscle. As a third cause of infarction, embolism must be mentioned, as for example, a detached bit of vegetation from bacterial endocarditis. No such instance occurred in this series, but there are rare examples reported.

In this study some degree of arteriosclerosis was found in the coronary system in every instance; most of the cases showed moderately to a markedly advanced lesions. In only one case (case 64) were there very slight sclerotic changes. Three other cases (cases 2, 14 and 59) showed moderate sclerosis, but there was little or no alteration in the size of the lumina of the vessels. In this group of 46 cases the point of occlusion was demonstrated in 35; a definite thrombus was the cause of the infarction in 23 cases, and in 12 the occlusion was due to the narrowing of the lumen of the arteriosclerotic vessel. In every instance where a thrombus was demonstrated, it was found to be attached to an underlying arteriosclerotic process. All of the features of arteriosclerosis were encountered, namely, tortuosity of vessels, inelasticity or rigidity of vessel walls, connective tissue proliferation, deposition of calcium salts and cholesterol, formation of atheromata with necrosis of the surface and thrombus formation. In one instance (case 21) in addition to other arteriosclerotic lesions, a small aneurysm was found in the circumflex branch of the left coronary. Syphilitic aortitis, as determined by histologic findings, was present in two

instances, cases 58 (Wassermann positive) and 66 (Wassermann negative). In both of these cases definite arteriosclerosis was also present, and in neither was the point of occlusion found.

The point of occlusion was found in various locations anywhere along the course of the vessels from their orifices, as a result of extensive aortic disease, to the very small arterial branches. Generally the nearer the orifice the block occurred the larger was the area of infarction likely to be. However, the area of damaged muscle was never as large as would be expected, taking into consideration the level of the closure and the area supplied by the vessel distal to the block. This, of course, is accounted for by the collateral circulation and anastomoses. Wearn (51) has reported some extraordinary cases in which both coronaries were entirely occluded at their orifices by aortic disease, and no infarction occurred. Death in both instances was sudden and the patients had previously been able to do a considerable amount of work. He ascribed the ability of these cases to maintain an adequate circulation to the aid given by the Thebesian vessels. It is reasonable and logical to suppose that when narrowing of the coronary arteries comes on gradually the Thebesian vessels may during this process take on this function of nourishing the heart, and in that way prevent the acute phenomena of sudden infarction of the heart. When the anterior descending or circumflex branches of the left coronary were the involved vessels, the occlusion was usually found within two centimeters distally to the bifurcation of these vessels. This was such a predominant location as to suggest that this region is particularly vulnerable to the development of an obstructive condition.

Enlargement of the heart is considered to be one of the best evidences of cardiac disease; this is particularly true in heart disease of a chronic nature. Cardiac infarction is acute in its symptomatology, but however acute the onset it must necessarily be an accident developing in the course of a chronic process (with the exception of the rare instances of embolism into the coronary artery). The question arises as to whether infarction ever occurs in a heart that is normal in size. Because in many of these cases the patient's condition was such as to entail an unnecessary hazard in getting the body weight, we have not the data to determine the body weight-heart weight ratio. We have, however, accepted the standard that an adult female's heart weighing

more than 350 grams and an adult male's heart weighing more than 400 grams are enlarged. In this series, in the females, the smallest heart weighed 260 grams, the largest 550 grams, with an average weight of 403 grams; in the males the smallest heart weighed 400 grams and the largest 810 grams, with an average weight of 557 grams. Accepting the above criterion of enlargement the hearts were not enlarged in five (10.8 per cent) of 46 cases.

It would be expected that in some instances we might come across cases in which recovery took place after one attack of cardiac infarction and that death occurred after a subsequent attack. It is conceivable that even more than two infarctions might occur in a single heart. In six of the 46 cases in this series there were both old and recent lesions. Not more than two infarctions were present in any heart. These cases seemed to follow no definite rule as far as the clinical picture was concerned. There might be no clinical story of the old infarctions, with a typical picture of coronary thrombosis to account for the recent lesion. Congestive heart failure might be present for months before the occurrence of the typical picture of infarction to account for the recent lesion found at autopsy. Both attacks might be associated with the typical pain and other findings; or there might be no pain at any time and the first or subsequent attack be signalled only by the presence of myocardial failure. It was impossible to determine accurately the time interval between the old and recent infarctions because of the atypical clinical features, but in all instances, with the possible exception of one, it seemed probable that the second infarction occurred within one year after the first. In four cases the old and the recent infarctions occupied widely different areas of heart muscle, and these were the best examples of recurrence. In two cases large scars were found within the area of recent infarction, and in these hearts there was no general scarring outside the area of infarction. This latter type of lesion might be considered as a delayed extension rather than a recurrence. In spite of the fact that two infarctions were found in the same heart, it could not be said that any more extensive arteriosclerosis was present than in some of the hearts showing only one infarction.

Healing of an infarction takes place by connective tissue proliferation and replacement of the damaged muscle by scar tissue. This cica-

trix, because of its size and strength, may or may not be sufficient to support the circulation. The scarred area may become very much thinned out and even develop into an aneurysm of the wall of the heart (cases 28 and 50). Nearly always mural thrombosis took place in the pouch of the aneurysm. Rupture may occur through the aneurysm (case 16). In this study there were eight cases in which there was a single infarction, old in nature, and in which healing had progressed to an advanced stage. The clinical picture was so atypical in many of these cases as to make it impossible to determine the time of infarction. In this group it was common for the actual event of infarction to be entirely masked by congestive heart failure. It would seem that the infarction occurred in the course of congestive failure in five of the cases, and could be said definitely to have developed after the infarction in three cases.

Congestive heart failure and cardiac infarction may be associated with two different sets of circumstances; firstly, the myocardial insufficiency that follows in the wake of an infarction that has been extensive enough to impair the circulation, and secondly, the development of infarction as an incident in the course of congestive failure due to some such conditions as so-called chronic myocarditis. Striking examples of each were encountered in this study. In the group representing the latter very often the occurrence of the infarction was almost or entirely masked by the picture of congestive heart failure, and this group furnishes many of the cases in which the diagnosis is difficult or impossible.

Most of the complications which may be associated with cardiac infarction have been mentioned already in some way in this section. Mural thrombosis occurred in a very high percentage of cases, and provided a rich source of embolism. Of course the thrombus which results directly from the infarction is attached to the area of damaged muscle. Emboli arising from mural thrombosis were found to lodge more frequently in the spleen, kidneys, brain and lungs than in any other parts of the body. Hematuria due to infarct of the kidney, hemiplegia due to cerebral embolism, infarcts of the spleen, with sudden pain in this region, and hemoptysis due to infarction of the lung may be explained on the basis of embolism. In one instance (case 136) the embolism lodged in the right popliteal artery causing gangrene.

Embolism lodging in the general arterial circulation would necessarily arise from the left side of the heart, while that affecting the pulmonary circulation would arise from the right side of the heart, providing there was no septum defect present. Effort has been made to determine by clinical criteria whether the left or right coronary artery was the site of the obstructive lesion causing the infarction. Embolic phenomenon would seem to supply some evidence. However, it is clear that this evidence may be fallacious because of the distribution of the coronaries; if the septum is involved in the infarction a thrombus may be formed in either the right or left ventricles or both as a result of a thrombosis of only the left coronary artery. Pulmonary infarction is not, therefore, critical evidence that the right coronary artery is occluded. Also mural thrombosis in the auricles may be found coincidentally. In this regard there were seven instances in the right auricle and two in the left.

Pericarditis occurred frequently but by no means invariably. There was gross evidence of it in 24 cases. It is a sterile process, except in a rare instance, and usually fibrinous in character with little serum. Not over 150 cc. of fluid were found in any case with pericarditis except in two instances where 1000 cc. and 400 cc. were found, and here it seemed that congestive heart failure may have accounted for the hydropericardium. The number of ruptured hearts in this series seems rather great, nine in 46 cases or about 19 per cent. Hemopericardium was always present, and as much as 750 cc. of blood (case 16) was found in the pericardial sac. Other complicating features encountered were congestive heart failure and pulmonary edema. Aneurysm of the wall of the ventricle at the site of the infarction was found in three cases (nos. 16, 28, and 50).

A survey of these 46 autopsies to determine any possible relationship of pain to anatomic or pathologic features is very interesting. Twenty-four cases had pain as a part of the clinical picture. In 22 of these the closure was in the anterior descending branch and in one in the circumflex branch of the left coronary. In the remaining case (case 37) the calcification of the coronaries was so marked that, in the absence of definite thrombus, it was difficult to ascribe the infarction to either vessel; the circumflex branch of the left seemed most at fault. It might therefore be said that in all of those in which

pain was a symptom there was occlusion somewhere of the left coronary artery. In neither of the cases of right coronary closure was there pain. Left coronary closure, however, was not always accompanied by pain as there were 20 cases without pain, 17 of these having the anterior descending branch and three the circumflex branch occluded. In some of these cases, to be sure, it was difficult to obtain an accurate description of the symptoms as the patients were too ill, and pain may well have been present. These are others, however, in which pain was quite definitely absent.

It had been thought that a sudden blocking of the circulation due to thrombus formation is more likely to be accompanied by pain than if the occlusion occurs as a result of a gradual arteriosclerotic process. In 16 of the 24 cases, closure was due to thrombosis, in the other eight to arteriosclerotic thickening. There were seven cases with closure due to thrombosis in which there was no pain. The degree of aortic disease about the orifices of the coronaries or elsewhere seemed to bear no definite relationship to pain. Twenty-one cases of the group of painful infarctions showed mural thrombosis and 15 pericarditis. Two cases that showed neither mural thrombosis nor pericarditis had pain. Several instances were found in which there was no pain even though pericarditis or mural thrombosis or both were present. Seven of the cases with rupture had pain at the onset of the illness and two did not. It might be said that the pain is generally but not invariably associated with the injury of the vessel wall and the subsequent inanition of the heart, rather than to the complications like pericarditis or mural thrombosis.

Pathologic findings outside the heart and associated with or coincident to the cardiac infarction were very variable, as might be expected. Chronic passive congestion of the viscera was common. Generalized arteriosclerosis seemed to follow no definite rule. Evidence of syphilis was infrequent, being found in only two cases. Gall stones with some degree of chronic cholecystitis were found in six cases. Only two of these cases gave past histories that were suggestive of gall bladder disease. Cholesterol deposits without stones were seen in the mucosa of the gall bladder in two cases. In six cases there was some type of pathology in the pancreas; the commonest finding being arteriosclerosis and interacinar fibrous thickening. Occasionally hyaline

degeneration of the islands of Langerhans was seen, and in one case there was fresh hemorrhage into the pancreas. There was no pain in this case. Glycosuria was present in some of these cases with pancreatic pathology and absent in others. Healed duodenal ulcer was found once and active peptic ulcer of the duodenum once. Diverticula of the duodenum were found in two cases. These duodenal lesions apparently had produced no symptoms. Renal lesion of vascular origin, such as renal arteriosclerosis, and chronic vascular nephritis, was encountered a number of times. Terminal pneumonia was present occasionally.

The findings in the heart valves were in general not remarkable. They frequently gave evidence of the same process of sclerosis that was found elsewhere. In 14 cases there was some degree of sclerosis of the valve leaflets of the aortic valve as manifest by slight fibrous thickening, atheromatous plaques or calcification. Similar changes were found in four cases in the mitral valve and in one case in the pulmonary-valve. There were no instances of true mitral stenosis and only one of aortic stenosis. Recently, however, one case of coronary thrombosis not included in this study was observed by one of us in a patient who had had for some years a definite rheumatic mitral stenosis.

VIII. SUMMARY

As a result of an analysis of the clinical features of 145 cases of coronary thrombosis and the pathological data of 46 of these, the following considerations were made.

1. Angina pectoris generally precedes attacks of coronary thrombosis, but there were a few instances in which it was quite clear that the patients not only had no angina but no evidence of any important preexisting disease could be made out.

2. Coronary thrombosis frequently developed in long standing mild diabetics, but because the age incidence was the same in diabetic as in non-diabetics it would seem that the diabetes merely indicated the type of individual who would develop coronary disease rather than that it had any causative relation to it.

3. Hypertension was present in the great majority of cases but in some it was quite definitely known that the blood pressure was normal

before the attack. Arterio-sclerosis was a very variable finding. In some it was strikingly limited to the coronary arteries.

4. Syphilis was found to be a very rare cause of coronary thrombosis, and other infectious diseases seemed to have very little etiological significance.

5. Hereditary factors, although extremely difficult to analyze, were found to be most important especially in those patients having coronary thrombosis at a comparatively young age. Possibly as a part of the hereditary factor there seems to be a certain physical type of indidual who is more apt to develop this disease. The type is that of a well set and strong individual, somewhat overweight, whose limbs and especially the forearms are round rather than flat. He generally has been quite active physically, either in sport or at work.

6. The average age in this series was 57.8 years. There were 111 males and 34 females. The marked disproportion in the sexes cannot be easily explained but brings up the possible relationship of physical work and tobacco to coronary disease, both of which factors are more prominent in the male than in the female.

7. The typical clinical picture of acute coronary thrombosis was discussed in detail. In addition certain atypical features were emphasized that are commonly overlooked and which are important in making a proper diagnosis. The pain was found to vary from a slight discomfort in the chest to the most terrific agony, and varied in the location from the upper abdomen to the upper sternum and throat. There were not infrequent cases that were entirely painless. It was emphasized that in some instances the entire picture resembles very closely an acute surgical abdomen. Although there customarily was a fall in the blood pressure with the attack, in some instances this did not occur.

Fever and leucocytosis developed early in most cases but there were rare exceptions. The temperatures must be taken rectally as the mouth readings were frequently normal when an actual fever was present. The important features on examination were the appearance of shock, the distant heart sounds, gallop ryhthm, the development of various irregularities in the rhythm of the heart, occasionally a pericardial friction rub, râles in the lungs and sometimes an engorgement of the liver.

Certain changes in the electrocardiograms were found to be invaluable as aids in diagnosis, both during the early days and also in the later weeks following the attack. Besides those electrocardiographic changes that have previously been described, attention was called to the development of a prominent Q wave in lead 3 in many of these cases.

The urine was frequently found to contain sugar and evidence of renal damage such as albumin and casts. At times there was marked oliguria or a suppression of urine. These findings generally were transient.

Both the types of death and the types of recovery, because of their variability, were analyzed and for the most part they were found to fall into fairly definite groups. This enabled one to predict somewhat more clearly the course of the disease.

8. The important conditions that at times had to be considered in differential diagnosis were an acute surgical condition of the abdomen, angina pectoris, pneumonia, diabetic acidosis, and finally so called chronic myocarditis. The proper diagnosis in most cases is possible, although to make it in some, all our methods of study including electrocardiograms may be necessary.

9. The criteria for prognosis in individual cases were found to be most unsatisfactory. In general about 50 per cent have an immediate recovery. No single feature seemed to be reliable as indicative of a good or poor prognosis. Apparently mild cases occasionaly died and very severe ones recovered. Slight differences in the mortality were found when certain factors were analyzed such as age, sex, the development of pericarditis, and auricular fibrillation. Ventricular tachycardia and heart block seemed to have a greater mortality than the average. Even the type of change in the electrocardiogram had no influence on whether the patient would recover or not.

10. The question of treatment for the present must be based partly on theoretical grounds as there are no data available to compare the end results of one regime with those of another. The acute and rapid character of the disease often makes our deductions as to therapy fallacious, because frequently many drugs are given in a short time and it is difficult intelligently to appraise the proper value of any single one. A proper understanding of the pathological process going on

during coronary thrombosis will help to some extent in rationalizing our therapy. Certain features in treatment were discussed which we consider may prove life-saving in occasional cases.

11. A careful pathological study of 46 of these cases was made. Apart from the ordinary findings some interesting correlations with the clinical features were uncovered. It was found that not infrequently a thrombus formed in the right ventricle as well as in the left as a result of a thrombosis of the left coronary artery. This happened when the interventricular septum was involved. There were two painless cases in which the right coronary artery was thrombosed. In nine cases rupture of the ventricle occurred. The most frequent artery involved was the left descending coronary and the favorite site of the thrombus formation was about 2 cm. below the bifurcation with the left circumflex coronary artery.

We wish to express our great indebtedness to Dr. Hugo O. Altnow of Minneapolis for the aid in compiling the data on the first forty cases here reported, and to the staff of the Peter Bent Brigham Hospital without whose co-operation much of the value of this study would be lost.

IX. CASE REPORTS

Case 1. Fig. 10. H. A. C. Male, 74. Had slight dyspnea for 8 months. Was seen May 5, 1915. Two days before this suddenly grew breathless and weak. No pain whatever. Examination showed distant grossly irregular heart sounds. Slight systolic murmur. No enlargement. There were râles at bases of both lungs. B.P. 100/70. Next day pericardial friction was heard and heart was regular. W.B.C. 16,900 (86 per cent neutrophiles). Urine—trace albumin and numerous granular casts. Temperature 98.6° to 100°F. E.K.G. showed small complexes in all leads and rounded, dipped T 2 and T 3. After two days he was doing well and feeling in good health. Died instantly May 9, 1915. Autopsy—almost complete occlusion of circumflex branch of left coronary artery, with rupture of left ventricle, and hemopericardium. This is a striking example of painless infarction.

Case 2. Fig. 72. L. T. Male, 54. Since an attack of pneumonia 5 years before, troubled with increasing dyspnea. Entered hospital January

18, 1921, with marked orthopnea. No pain in chest. Heart markedly enlarged. B.P. 185/130 (1915—130/90; 1916—170/104). W.B.C. 16,000 to 23,000. Urine—large amount of albumin and numerous casts. Temperature 99° to 101°F. Pulse 100 to 110. E.K.G. showed slight spread in the Q R S complex. He ran the course of a chronic progressive nephritis, blood pressure falling to 138/95, and died March 3, 1921. Autopsy—mural thrombus in left ventricle; coronaries sclerosed but not occluded; portion of left ventricle recently infarcted; acute pericarditis. This illustrates a type of cardiac infarction occurring without pain in the course of a chronic vascular nephritis.

Case 3. Figure 71. J. T. Male, 59. Slight dyspnea of one year. Was in very good health up to 4 hours before entering hospital June 6, 1916, when he was taken with a sudden excruciating pain in the epigastrium and vomited. Physical examination showed a patient in collapse with shallow, rapid breathing; cold, clammy, ashen-colored skin; upper abdomen rigid. Heart sounds distant; rate 104; gallop rhythm; no murmurs; marked tenderness in epigastrium and right upper quadrant. Over right lower lung breath sounds diminished and many râles. W.B.C. 20,000 to 33,500. Urine—1 to 2 per cent sugar and a rare cast. Temperature 99.4° to 100.2°F. B.P. 106/80. At first it was thought that patient had an acute surgical lesion of the upper abdomen, such as acute pancreatitis or ruptured gastric ulcer. Just before he was about to be operated on, complete heart block with rate of 29 developed and diagnosis of coronary thrombosis was made. Died June 8, 1916. Autopsy—occlusion of anterior descending branch of left coronary artery; infarction of left ventricle with mural thrombus. This case illustrates the type that is so often called acute indigestion, and for which abdominal operation is occasionally performed by mistake.

Case 4. Fig. 64. W. S. Male, 63. Entered hospital September 12, 1917. Nine days before, after a strenuous mountain climb, followed by a hearty meal, was taken with severe pain in center of chest, radiating to both arms. This was not relieved by nitroglycerine or by morphia for four days. Physical examination showed shallow, rapid breathing; heart sounds almost inaudible; coupling of beats; many râles at bases of lungs. W.B.C. 24,000 to 34,500. Urine—small amount of albumin, numerous casts and 3 per cent sugar. Temperature 97.4° to 99.2°F. Pulse 144 to 110. Dyspnea persisted. E.K.G. showed very small complexes and every third beat was a ventricular extra systole. He developed evidence of increasing congestive heart failure and died September 13, 1917. Autopsy—occlusion

of descending branch of left coronary artery, fresh pericarditis (no friction rub heard during life), large infarct of left ventricle and interventricular septum with mural thrombus. This case is rather typical in its course and illustrates an onset after unaccustomed exertion and a hearty meal.

Case 5. Fig. 31. J. H. Male, 60. For two years there was increasing dyspnea, especially nocturnal. Two weeks before entering hospital, April 13, 1918, signs of congestive heart failure developed. Heart showed distant sounds, tic-tac rhythm, peripheral edema, râles in the lungs, dullness at right base and mental symptoms. Evidence of heart failure improved, but later grew worse again about May 21, 1918. Then there developed leucocytosis of 26,000. Temperature 101° to 103°F. B.P. ranged around 170/115. E.K.G. not remarkable except for presence of extra systoles. He developed left facial paralysis and aphasia and died July 14, 1918. Autopsy—thrombosis of right coronary artery; infarction of diaphragmatic surface of apical region involving both right and left ventricles; mural thrombus in both ventricles; infarcts in lung and spleen. This case illustrates infarction of heart incidental to congestive heart failure.

Case 6. Fig. 28. D. G. Male, 59. Had angina pectoris for 8 or 10 years. For 2 months before entering hospital July 30, 1918, there was increasing edema and nocturnal dyspnea. Physical examination showed enlarged heart; distant sounds; frequent extra systoles. There was an enlarged liver, hydrothorax. B P. about 160/105. Leucocytosis developed during his stay. Temperature 100° to 101°F. on several occasions. E.K.G. showed curves of very low amplitude. August 6, 1918, he had a sudden dyspneic and unconscious spell lasting 40 minutes. He never had chest pain and gradually failed and died with pulmonary edema on August 19, 1918. Autopsy—thrombosis of descending branch of left coronary artery, mural thrombus in left ventricle. The impression from the pathological study was that the coronary thrombosis was slow in forming, over a period of some months. This case apparently developed a painless infarction of the heart as a part of the picture of general myocardial insufficiency.

Case 7. Fig. 13. C. C. Female, 68. Rheumatic fever at 35. Some dyspnea and edema for one year. Two weeks before admission, October 18, 1920, severe knife-like pain in chest lasting 2 days. Marked dyspnea since then. Physical examination showed distant heart sounds, loud systolic murmur, moist râles at both bases. B.P. 185/85. No leucocytosis. Temperature 99.8° to 101°F. While in hospital there was no chest pain

but marked dyspnea, out of proportion to other evidences of heart failure. E.K.G. not remarkable. Died suddenly October 28, 1920. Autopsy showed first portion of descending branch of the left coronary artery was almost occluded by calcified plaques and a thrombus. There was a mural thrombus in the left ventricle. This case illustrates an instance in which marked dyspnea is the outstanding feature. Blood pressure remained elevated throughout and electrocardiograms were not strikingly abnormal.

Case 8. Fig. 15. A. D. Female, 42. Patient was in good health until 4 days before entry to hospital, October 25, 1920, when she had a severe "tearing" pain in left chest and left arm, continuing for several days. Physical examination showed a very restless woman with marked respiratory distress. Heart sounds distant. Apex impulse not seen or felt. Many râles in bases of both lungs. B.P. 100/70. Slight icterus of sclerae. W.B.C. about 20,000. Temperature 101°F. Pulse 110 to 140. E.K.G. showed curves of low amplitude. Patient presented the picture of severe obscure infection, although the ante-mortem diagnosis of coronary thrombosis was made. Sudden death July 27, 1920. Autopsy showed infarct of left ventricle, mural thrombus and rupture of the heart. The descending branch of the left coronary artery was thrombosed. This case illustrates a type which might have been confused with pneumonia.

Case 9. Fig. 29. M. H. Female, 55. Dyspnea on exertion for 1 year. Angina pectoris for 3 months. Three days before entry, January 26, 1921, severe pain in center of chest, persistent with slight intermissions, vomiting and perspiration. Physical examination, pale, ashen facies, and shock-like expression. Heart regular and rapid with gallop rhythm. Sounds faint, sudden halving of the rate (heart-block). W.B.C. 15,000 to 25,000. Temperature 101° to 102°F. for three days, then normal. B.P. 150/100 (January 26, 1921); 80/60 (January 29, 1921). Many râles at base of right lung. Numerous attacks of unconsciousness and weak spells. Pulmonary edema increased. Electrocardiograms showed many peculiar changes in rhythm and in type of complexes. Sudden death February 7, 1921. Autopsy: showed almost complete closure of the left coronary artery, infarction of left ventricle and interventricular septum and mural thrombus of left ventricle. This was a typical case. Death was sudden although no rupture occurred. This may have been due to a sudden standstill of the heart in the nature of heart-block.

Case 10. Fig. 51. I. M. Female, 63. Palpitation many years. Slight dyspnea. Gall stone attack 6 years ago. One and one-half years mild

diabetes. For 6 weeks before admission, July 8, 1921, typical anginal attacks with increasing dyspnea. 18 hours ago sudden severe chest pain arousing patient from sleep. Unrelieved by morphine. P.E.: B.P. 6 months before 220/120. After severe attack 142/90. Rapid, regular heart; sounds distant. No murmurs or friction. Patient seemed to be in shock. E.K.G. showed slight high take-off in T. 1. Curves were distinctly different from those obtained 6 months previously. Died few hours after entry. Autopsy showed rupture of left ventricle through fresh infarct. Case was rather typical occurring in one with previous diabetes and angina.

Case 11. Fig. 8. G. B. Male, 64. In past years several attacks of gout. For 1 to 2 years some dyspnea, and anginal attacks. Occasional nocturnal dyspnea. For 4 days before admission June 10, 1921, angina more troublesome and for 2 days slight constant chest pain. On morning of admission awoke out of sound sleep with extreme suffocation and presented picture of mild acute pulmonary edema. P.E. showed regular heart with loud systolic murmur; apex impulse not seen or felt. Râles at right base. Temperature 101° to 102°F. for 4 days. W.B.C. around 30,000. Some of the features brought up question of pneumonia. B.P. which was 200/110 before the attack gradually fell to 110/75. E.K.G. showed curves of low amplitude. Patient improved until the 12th day when he died suddenly. This case illustrates the type that begins with acute pulmonary edema and later looks like pneumonia.

Case 12. A. M. Male, 69. For 3 months before admission July 14, 1921, there were typical anginal attacks. P.E. not remarkable except for peripheral arterio-sclerosis and somewhat distant heart sounds. B.P. 168/88. Two days after admission constant precordial pain began; slightly relieved by nitroglycerine. This continued for two days when he suddenly died. Autopsy showed infarction of left ventricle and fresh thrombosis of the anterior descending branch of the left coronary artery. This case is rather typical, developing in the hospital where patient came to be treated for angina pectoris.

Case 13. J. J. B. Male, 61. For a few months he had cough and some blood streaked sputum. For two months before admission December 1, 1921, there was marked dyspnea. P.E. showed cardiac hypertrophy, poor heart sounds, slight systolic murmur at the apex, marked radial and retinal arterio-sclerosis. There was considerable peripheral pitting edema. He presented a picture of chronic myocarditis with generalized circulatory

failure. He improved considerably for a few weeks under treatment and then he began to have severe precordial pain. Two days after this W.B.C. was 9700. Pulse became irregular and gallop rhythm was heard. Temperature rose to 101.4°F. B.P. was 180/130 before the attack of pain. Several days after the first attack of pain there was another severe attack, and a few days later a third. With this there was marked collapse and patient died. Autopsy showed infarction of left ventricle with a mural thrombus. There were old and recent infarcts of the spleen. This case illustrates the development of coronary thrombosis in a patient with chronic myocarditis with congestive heart failure.

Case 14. Fig. 23. H. W. F. Male, 54. For two years had increasing dyspnea. For 6 months troublesome indigestion. Also attacks of palpitation supposedly transient auricular fibrillation. On the day of admission May 10, 1922 P.E. showed markedly enlarged heart, systolic murmur over precordium, congestive râles at both bases. B.P. 175/100. Temperature 101.2°F. W.B.C. normal. Dyspnea was most striking complaint. There was no pain. E.K.G. not particularly remarkable, and were not unlike those taken 5 months before he died. Patient seemed to be improving with digitalis and other treatment, until the 4th day when he suddenly died. Autopsy showed old infarct of left ventricle at apex with mural thrombus. This case illustrates occurrence of infarction of heart without any definite feature in the history indicating its onset, in a patient who had congestive heart failure.

Case 15. Fig. 1. B. A. Male, 61. For 10 years there was indigestion; for $1\frac{1}{2}$ years cramps in the legs. For one week a sense of fatigue and slight shortness of breath. On day before admission, July 7, 1922, there was severe pain in the epigastrium and belching of gas. This was followed by diarrhea. Pain was severe and unrelieved by nitroglycerine. P.E. showed a restless man. Heart negative; sounds were of good quality. B.P. 110/78. W.B.C. 13,450. Urine showed 2.3 per cent sugar which disappeared in several days. Temperature 100°F. for three days. E.K.G. showed minor changes in the T wave. Patient improved although during the early days the blood pressure fell to 90/58. Recovery was satisfactory. This case illustrates the type that is often called acute indigestion or ptomain poisoning.

Case 16. Fig. 30. F. W. H. Male 63. Conscious of irregular heart action for one year. No previous dyspnea or angina. Fourteen days be-

fore admission July 18, 1922 typical attack of severe chest pain with collapse lasting over a day. Followed by spells of weakness and faintness. P.E. showed considerable peripheral arterio-sclerosis. Apex impulse not seen or felt. Sounds very distant. B.P. 110/74. Many moist râles over both lower lobes. Eight days later definite pericardial friction rub and gallop rhythm heard. Signs suggestive of pulmonary infarct developed. He had a good deal of chest pain during the following two weeks and spells of weakness. Later a definite systolic murmur heard and left border of the heart was made out 2 cm. outside the nipple. Throughout his stay there was a leucocytosis and a temperature around 101°F. E.K.G. showed a slight high take-off of T l. Died suddenly 5 weeks after the onset. Autopsy showed rupture of the heart and mycotic aneuysm of the left ventricle with mural thrombus. There was no pulmonary infarction. This case had a typical onset but in the subsequent course the conspicuous feature was the pulmonary complication which clinically was thought to be due to pulmonary infarction but which proved to be due to edema of the lungs.

Case 17. Fig. 3. M.B. Male, 49. Paroxysm of cough for 20 years. Three years ago severe chest pain lasting two days. Less severe attack one year ago with dyspnea. Five days before admission October 4, 1922, very severe chest pain with extreme dyspnea. Frequent spells since then. P.E. showed extreme dyspnea with marked perspiration. Heart sounds very distant and of tic-tac gallop quality. Numerous moist râles throughout chest. B.P. at first 150/110; two weeks later 90/68. W.B.C. 19,200, which gradually fell to normal. Urine showed large trace of albumin, with numerous casts which almost entirely cleared up after a week. Temperature 102° to 100°F. for first 5 days. E.K.G. showed coarse notching and curves of low amplitude. Patient gradually recovered very satisfactorily. He died 4 years later. This case ran a typical course which showed striking dyspnea. History suggests that the previous attack was one of coronary thrombosis.

Case 18. Fig. 14. C. W. C. Male, 69. Diabetes for 15 years. Slight dyspnea for 10 years. Angina for 7 years. Seven and four days before admission December 1, 1922 attacks of severe chest pain, which three days ago became constant. Pain then changed to feeling of dull aching over precordium. There was marked sweating, exhaustion and dyspnea. P.E. showed marked enlargement of heart, regular rhythm, and sounds of fair quality. Many moist râles throughout the lungs. B.P. 112/70. Day after admission heart sounds became distant. Next day marked Cheynes-

Stokes breathing developed. Auricular fibrillation noted the second day. W.B.C. 17,300. Later, 15,900. Urine: Specific gravity 1032, slight trace of albumin, numerous hyalin and granular casts, 2.2 per cent sugar. Temperature reached 103°F. E.K.G. showed high take-off in T 1 and T 3 with sharp inversion. He died with picture not unlike uremia. Autopsy showed a slight pericarditis, infarcted left ventricle with large mural thrombus. There were infarcts in the lungs and spleen. This patient had a typical onset with gradual exitus presenting cerebral symptoms as in chronic renal insufficiency.

Case 19. Fig. 68. A. S. Female, 60. Patient was mild diabetic of some years standing with intermittent claudication of the legs. August 26, 1922 had repeated paroxysms of cramping, knife-like pain in the chest, which then became constant and lasted 2 days. Considerable belching of gas. Pains radiated into the arms and wrists. W.B.C. 11,300 and 16,700. Temperature 100° to 101°F. for a few days. E.K.G. showed sharp inversion of T 1. Patient showed many neurotic symptoms which somewhat masked the real condition, but she gradually recovered and became ambulatory. January 14, 1923 an attack similar to the above developed, associated with vomiting and incontinence. Heart sounds were feeble with tic-tac quality. There was a slight systolic murmur. B.P. 160/86. Râles over the right base. Slight leucocytosis and fever. Chest pain continued; not relieved by nitroglycerine. E.K.G. now showed distinct changes over the previous ones. There was typical high take-off of T 2 and T 3. Dyspnea was absent. Death was gradual February 3, 1923. In this case there were apparently two major attacks and during the first one the true condition was masked by prominent neurotic symptoms.

Case 20. Fig. 7. A. B. Female, 70. Patient had had a good deal of indigestion and for one month had complained of a pain in the upper chest, shoulders and arms. On admission, May 8, 1923, heart was regular, sounds faint. No râles in the lungs. W.B.C. 13,000. Temperature 101°F. B.P. 145/80. May 6, 1923 she had a sudden left-sided hemiplegia. Before this the diagnosis was obscure. This brought up the question of coronary thrombosis. E.K.G. showed prominent inversion of T 1 and T 2, and a well marked Q 3. Patient gradually died May 22, 1923. Autopsy showed infarction of left ventricle, mural thrombus, and infarct of brain. In this case the diagnosis at first was obscure because of poor history. The embolic phenomenon directed attention to the correct underlying condition.

Case 21. Fig. 73. A. J. T. Male, 58. For 10 months there was increasing dyspnea. Two months ago two severe anginal attacks. Six weeks ago congestive heart failure. Four weeks ago hematuria. At times he was irrational. Congestion improved and 2 days before admission September 14, 1923 pulse became very weak, delirium, edema and dyspnea developed. No pain. P.E. showed heart sounds of good quality and regular; dullness both bases, probably due to fluid; liver markedly enlarged. B.P. 98/66. Patient grew very restless and irrational. W.B.C. normal. Temperature 99.4°F. E.K.G. not remarkable. He died September 26, 1923. Autopsy showed infarction of apex of heart involving left ventricle and septum apparently of several weeks duration, mural thrombi in right auricle and both ventricles, and pulmonary infarct. Here cardiac infarction seems to have developed in a patient with advanced cardiac failure, which masked the diagnosis.

Case 22. Fig. 77. J. F. W. Male, 65. One and one-half years ago marked dyspnea developed and edema of feet and ankles. At this time, he showed the picture of advanced cardiac failure which improved satisfactorily on treatment. Later prostatectomy was done. He did quite well until 10 days before admission, October 25, 1923. Marked dyspnea returned. Heart markedly enlarged; sounds were distant; occasional extra systoles. Three weeks later he had a chill, fever, and there was a pleural friction rub, suggesting pulmonary infarct. Several days later auricular fibrillation suddenly developed. Throughout this time there was a constant leucocytosis from 12,000 to 25,000. B.P. ranged around 135/90. He ran an irregular fever up to 102°F. after the pulmonary infarction. E.K.G.'s were not remarkable and no appreciable change occurred during the $1\frac{1}{2}$ years of observation. He died gradually with advancing signs of disease of the lung. Autopsy showed infarcts of both lungs and right kidney. Descending branch of left coronary artery almost occluded, and there was a mural thrombus in the left ventricle. There was a thrombus in right auricle but none in right ventricle. This is a case of cardiac infarction without pain in a patient who has had general circulatory failure. It also illustrated that pulmonary infarction may occur without thrombi in the right ventricle.

Case 23. S. F. Male, 65. Had angina for 2 years and dyspnea for 6 months. For 2 weeks before admission, October 31, 1923, attacks of chest pain were more severe and frequent. The pain was localized under the sternum and did not radiate; it tended to remain constant and was not relieved by nitroglycerine. He was cyanotic and in evident distress. Heart

moderately enlarged. Sounds of fair quality; frequent premature beats. Many râles over both bases. B.P. 145/105. W.B.C. 16,400. Urine showed numerous hyalin and granular casts. Temperature 100°F. Substernal pain persisted a week. E.K.G. showed a rounded R-T interval. He gradually improved and was discharged in good condition. He died 3 years later. This is a fairly typical case with satisfactory recovery.

Case 24. Fig. 46. J. J. M. Male, 64. Had attacks of chest pain for 10 to 12 years. Indigestion 15 years. Dyspnea for one month. Three weeks before admission March 1, 1924, he had severe precordial and epigastric pain with fear of death. Pain lasted several hours. Next day pain returned, persisted for 3 days, radiated to left arm and left scapula. Not relieved by any medication. P.E. showed heart slightly enlarged, sounds of normal quality, later became very distant; definite pulsus alternans and a moderately loud systolic murmur. W.B.C. 8,000. Temperature normal. There was a slight fever on several occasions when attempts were made to get the patient out of bed. E.K.G. showed typical high take-off of T 1. Patient improved, became ambulatory and felt fairly well. He dropped dead one year later while walking on the street. This is a typical case with recovery coming in a patient with a long history of previous angina.

Case 25. W. H. F. Male, 56. For two and one-half years slight dyspnea. Two and one-half months ago questionable shock causing left-sided hemiplegia with complete recovery. 5 days before admission April 1, 1924, severe pain began in right lower chest, extending to precordium; lasted 24 hours and then returned. Then radiated to the left arm and to epigastrium. There was pain on swallowing and this radiated down the sternum. P.E. showed moderate cardiac enlargement, grossly irregular rhythm (rhythm was regular 3 weeks before). Sounds of good quality. B.P. 160/110. Râles over both lungs. No enlargement of liver or peripheral edema. W.B.C. 22,500. Gradually fell to normal in one week. Temperature 100°F., for 2 days. Slight trace of sugar in the urine. Patient gradually improved and became ambulatory. Died about 8 months later. This case was unusual because of the wide distribution of the pain, especially involving the epigastrium; also the auricular fibrillation which developed, persisted.

Case 26. Fig. 75. A. A. W. Male, 50. Six months ago had severe chest pain under the sternum. Since then a good deal of gas and indigestion, relieved by soda. One month ago chest pain returned. Four days before

admission April 13, 1924 severe persistent pain developed in the chest radiating to the left arm and elbow, accompanied by cold sweats and pallor. Patient seemed apprehensive, cyanotic and still suffering pain. Heart sounds weak and distant with slight systolic murmur. Râles present at the bases. Pericardial friction rub was heard. W.B.C. 19,800. Two days later 9,300. Temperature 100° to 101°F. for first 2 days. B.P. 134/98. Five days later 112/88. E.K.G. showed typical high take-off in T 1 and T 2. Because of the marked gastric symptoms and history of indigestion, patient had gastro-intestinal and gall-bladder x-ray studies and was allowed to be out of bed despite the electrocardiographic diagnosis of coronary thrombosis. April 23, 1924, while doing well, was taken with severe epigastric pain and died within a few minutes. Autopsy showed pericarditis, thrombosis of descending branch of left coronary artery and left ventricular mural thrombus. In this case, the electrocardiographic data was really the most critical point in the diagnosis and at that time we considered it wrong to disregard such a typical finding.

Case 27. Fig. 80. W. E. Y. Male, 58. Diabetes for six years. One week before admission May 6, 1924 marked dyspnea, epigastric distress, and pain in the upper abdomen developed. Few days later swelling of the legs and cough. P.E. showed striking respiratory distress, ashen-grey color to the skin. Heart sounds of poor quality, definite gallop rhythm and moderate enlargement. Many râles over both bases. Evidence of consolidation of right lower lobe. Liver enlarged. B.P. ranged from 100 to 115 systolic and from 60 to 70 diastolic. May 9, 1924, circulatory collapse following bed bath; then showed transient fibrillation. The striking feature was the appearance of shock and very distant heart sounds. W.B.C. 13,000. Temperature 100°F. Glycosuria 3.3 per cent. E.K.G. showed slight spreading and notching of the Q-R-S waves. Patient gradually recovered and became ambulatory after 3 months. In November 1924 he died suddenly while at stool. This case was rather typical with immediate recovery.

Case 28. Fig. 40. F. L. Female, 44. For seven years slight dyspnea. Two years indigestion and pain in chest, most marked half hour after meals. Five days before admission June 2, 1924, severe pain in left elbow, shoulder and hand, later extending into the chest and through to the left scapula. This remained intense for 3 days, but has continued in a milder form since. On the fourth day after the onset, pericardial friction rub was heard. Patient presented an agonized expression to the face, still suffering

pain. Marked cyanosis. Heart slightly enlarged; marked precordial hyperesthesia. Heart sounds muffled. Soft apical systolic murmur. Râles at both bases. Marked retinal arterio-sclerosis. B.P. 1922, 195/120. June 19, 1924, 180/120. June 22, 1924, 106/80. W.B.C. 19,600. Leucocytosis persisted for 1 month. Temperature 103°F. Gradually fell to normal in one week, with a secondary rise to 100°F. for one month. Patient had several attacks of transient fibrillation. E.K.G. showed typical high take-off in T 2 and T 3 and marked Q 3. Patient ran a very stormy course. July 3, 1924 developed signs of pulmonary infarct, with pleural friction on the left. Left hydrothorax developed requiring thoracentesis. Gradually improved and became ambulatory after 3 months illness. April 10, 1926 had a right hemiplegia. Hypertension returned, B.P. 210/135, November 14, 1926. During the winter of 1926 she developed congestive heart failure and died on February 6, 1927. Autopsy showed obliterated pericardial sac due to adhesions, almost complete occlusion of descending branch of left coronary artery, aneurysm of the apical portion of left ventricle, and mural thrombus in the aneurysm. This is a typical case of recovery resulting in aneurysm of heart and congestive failure.

Case 29. Fig. 17. H. D. Female, 70. Angina for 4 years. Good deal of indigestion relieved by soda. One year ago severe attack of chest pain which may have been an attack of coronary thrombosis. For 3 weeks the angina and dyspnea were more marked. Two days before admission July 22, 1924, while stooping over the heart began to beat rapidly. There was extreme weakness and patient broke out in cold perspiration. The next day very severe chest pain radiating into left arm. Patient somewhat irrational and showed marked respiratory distress. Apex impulse not seen or felt. Heart sounds very distant. Moist râles both bases. B.P. 125/75. Definite pulsus alternans. W.B.C. 22,600. Urine showed s.p.t. albumin and many fine brown granular casts, s.p.t. sugar. Temperature 100° to 101°F. E.K.G. not remarkable. The condition was at first considered to be pneumonia but on careful analysis of the history the diagnosis of coronary thrombosis was made. Patient died of circulatory failure with marked respiratory distress. Autopsy showed occlusion of descending branch of left coronary artery, mural thrombus and infarcts of both kidneys. This is a fairly typical case in all respects and illustrates the fact that the condition may resemble pneumonia.

Case 30. Fig. 16. S. P. D. Male, 36. Has had a good deal of indigestion relieved by soda. Some 15 years previously a questionable primary

luetic infection. Two weeks before admission August 3, 1924 had slight dizzy spell in the morning and that evening had terrific pain in chest, extending down left arm to the fingers and to the right elbow. Continued for 5 hours. Morphia gave no relief. There was slight dyspnea with this. Next day went to work although he still had pain in the left shoulder. Was ambulatory until put to bed in the hospital. Heart not enlarged; apex impulse seen and felt, 9 cm. to the left. Sounds of good quality; no murmurs. B.P. 115/80. July 27, 1924, W.B.C. 15,000. August 11, 1924, W.B.C. 8,200. Temperature normal. Blood Wassermann strongly positive. August 24, 1924 sudden definite weakness—right side of face and numbness of right arm. This cleared up in two days. E.K.G. showed typical high take-off of T 1 which became sharply inverted. He received mercury inunctions and potassium iodide but no intravenous arsenic. Uneventful recovery and has been well and at work for the past $3\frac{1}{2}$ years. This case was first seen in private practice 10 days after the attack while the patient was feeling quite well. The E.K.G. which was so typical was very helpful in making the diagnosis. The extremely young age in this case may be accounted for by a syphilitic background.

Case 31. J. P. Male, 70. Three weeks ago slight swelling of the ankles. One week ago known to have a high blood pressure. Three hours before admission August 12, 1924 severe epigastric pain, vomiting, collapse. Later had pain in the chest and marked prostration. P.E.—marked cyanosis and Cheynes-Stokes breathing. Heart considerably enlarged; sounds very distant. Blood pressure, 100/60. E.K.G. showed a high take-off of T 2 and premature auricular beats. Patient died in 4 hours. This case is rather characteristic of the type one reads about in the newspapers of a prominent man dying of acute indigestion.

Case 32. Fig. 45. L. M. Female, 63. For 8 years there was some dyspnea and an occasional chest pain. For 6 years frequent spells of unconsciousness, associated with vomiting. Was in the hospital twice previously for the above symptoms. Two days before admission October 30, 1924, after an unconscious spell and vomiting, had an attack of severe vice-like pain in the center of the chest and epigastrium. Heart moderately enlarged; sounds quite faint; soft systolic murmur at apex. B.P. 94/48 (1 year ago 170/80). Many moist râles at both bases. W.B.C. 11,000. Temperature 100° to 101°F. during first week. E.K.G. showed a distinct change in T 1 and T 2 over those taken a year before. They also showed partial heart-block. Patient gradually recovered but died about $2\frac{1}{2}$ years

later. The features in this case are somewhat atypical because of the underlying symptoms of cerebral sclerosis and chronic myocarditis.

Case 33. Fig. 12. M. C. Male, 47. Slight increase of dyspnea for 3 years. Angina attacks for 2 years. Relieved by nitroglycerin. Morning of admission, November 11, 1924 sudden severe pressure in the chest, radiating to the left shoulder and arm. There was marked perspiration and shortness of breath; later vomited. 2 injections of morphine without relief. Patient was quite dyspneic and cyanosed with a pale anxious expression. Heart markedly enlarged; loud high-pitched systolic murmur all over precordium. Sounds faint. Definite pulsus alternans. Many râles throughout both bases. Liver palpable and tender. B.P. 102/82 (November 11, 1924). 92/72 (November 13, 1924), 3 months ago B.P. 130/90. W.B.C. 22,400 to 19,700 during first week. Temperature 100° to 101°F. E.K.G. showed coarse notching of Q-R-S and low amplitude of curves. Patient gradually grew worse, became irrational, developed Cheynes-Stokes breathing, increasing dyspnea and died November 20, 1924. This was a typical case in which there was marked dyspnea.

Case 34. Fig. 39. M. L. Female, 56. For 24 years slight dyspnea on exertion. 2 weeks ago very severe occipital headache which lasted for a week and disappeared after a copious nasal discharge. 4 days before admission February 1, 1925, became dyspneic in bed. 2 days later collapsed and became pulseless on walking to the toilet. Some nausea. Heart not enlarged; apex impulse not seen or felt; sounds were distant; definite presystolic gallop rhythm at apex; slight systolic murmur; few râles at bases of lungs. B.P. February 1, 1925, 150/105; February 5, 1925, 120/70. W.B.C. 22,400 February 1, 1925, 9,900 February 4, 1925. Temperature 100°F. for first 5 days. E.K.G. showed typical high take-off, T 1 becoming sharply inverted. Patient improved; eventual outcome could not be ascertained. This was essentially a painless type of case in which the history of marked sudden dyspnea, the typical electrocardiograms, distant heart sounds with gallop rhythm, and the leucocytosis, made the diagnosis.

Case 35. Fig. 42. D. F. M. Male, 48. 10 years ago had an attack of indigestion, constriction in the chest, and perspiration; since then milder spells usually coming after large meals. On the day before admission, January 23, 1925, while pouring acid on some metal during his work, he inhaled some toxic fumes, became weak, dizzy and felt constriction in the chest and dropped in a faint. At the hospital he was semi-stuporous, cya-

notic, almost pulseless; heart sounds were very faint. B.P. 95/75. The next day the evidence of shock cleared up and face was florid. Many coarse râles both bases; left lower chest dull and harsh; pleural friction was present. W.B.C. 22,300, January 23, 1925. It came down to normal on daily counts on February 3, 1925. Temperature 102°F. first 4 days, then gradually returned to normal. E. K. G. showed partial heart-block the first day, but later showed striking and typical changes in the R-T intervals in Leads 2 and 3. B.P. remained under 100 systolic most of the time. Patient made a splendid recovery and except for an occasional attack of chest pain, has been in fair health and working for 3 years. The interesting feature here is the onset of the attack in the relation to the inhalation of toxic fumes. It was definitely shown that leucocytosis could last 11 days. Electrocardiograms were the most striking ones of the entire series.

Case 36. Fig. 52. P. N. Male, 72. Chancre treated with mercury at age of 36. For 1 year suggestive history of angina. For 4 months dyspnea on climbing stairs. Four days before admission, February 26, 1925, while at a motion-picture theatre was taken with a sharp knife-like pain beneath the sternum, radiating through the left chest, then became short of breath; walked home with assistance. Pain persisted for 4 days, aggravated by a cough. Heart showed a weak, first sound, definite systolic murmur; lungs and liver negative. B.P. 145/85 February 26, 1925. 128/70 March 1, 1925. Gallop rhythm developed. W.B.C. 8,600 February 26, 1925. Temperature 100.8°F. E.K.G. showed a suggestive change in T 3. While doing fairly well patient instantly died without pain. Autopsy showed hemapericardium, rupture of the posterior portion of the left ventricle through an infarcted area, and also a mural thrombus. This case was typical in every respect.

Case 37. Fig. 81. C. Z. Male, 69. Moderate dyspnea for 2 or three years. Two weeks ago substernal oppression lasting 3 hours. More dyspneic since. Twenty-four hours before admission, December 29, 1924, severe attack of substernal pain, becoming a dull ache with hyperesthesia of the precordium. Vomited 3 times. Patient showed drawn features and ashen face. Heart enlarged; sounds distant; gallop rhythm present; moist râles at both bases; liver 3 cm. below costal margin and tender; B.P. 104/80. W.B.C. 7,900. Temperature 100° to 101°F. E.K.G. showed slight spreading of the Q-R-S and atypical T waves. Patient gradually died with dyspnea December 30, 1924. Autopsy showed infarct of the posterior wall of the left ventricle, extreme coronary sclerosis and bilateral

pleural effusion. This case was typical. It is interesting that the W.B.C. was normal, although there was distinct fever. (This was also true in case no. 36.)

Case 38. C. Y. Male, 56. 5 months ago right side of head and body became numb and weak. For several months, marked nocturia. For 2 weeks edema of right leg. Gradual increasing weakness. Heart somewhat enlarged; blowing systolic murmur. Marked peripheral arterio-sclerosis. B.P. 215/130 February 28, 1920: 190/130 March 17, 1920. W.B.C. normal. Temperature normal with slight rises during last ten weeks of life. Patient grew weaker, became stuporous, and died gradually March 30, 1920. Autopsy showed infarct of the left ventricle with mural thrombus; coronary arteries were markedly sclerosis and narrowed, but patent. There was also evidence of chronic nephritis. This was an instance of silent infarction of the heart occurring in a patient with extensive vascular disease producing hypertension and nephritis. It is interesting that the blood pressure remained at a high level.

Case 39. Fig. 6. J. B. Male, 50. Patient was always strong, vigorous and active. On the day before the severe attack, April 8, 1923, there were a few premonitory anginal spells. On this night he was suddenly taken with terrific constriction of the chest without radiation. He received $1\frac{1}{2}$ grains of morphia hypodermically, but the pain was intense for 5 hours and it gradually let up. With this there was marked pallor, sweating and collapse. Heart sounds were distant and tic-tac in quality. B.P. 180/110 the day before the attack; after this it was very low and even a year later was 130/85. Temperature 100°F. for a few days. Pulse rate 120 for a week and around 100 for several weeks there after. E.K.G. not obtained during the attack, but were not striking the day before the attack. He was desperately ill and ran a stormy course. On April 15, 1923 had a severe attack of pain in the left flank, radiating to the testes, and followed by hematuria. This was probably a renal infarct. He then gradually improved and afrer 10 weeks illness, returned to work. He remained in very good health, and died suddenly 3 years later. The interesting features here are the absence of any preceding history of angina except on the one day before the attack, the extreme pain, the development of a renal infarct, and the excellent recovery.

Case 40. Fig. 47. J. K. Male, 42. Patient was a vigorous athletic man; definite angina for 4 months. While in bed, being treated for angina

pectoris, June 3, 1923, he suddenly had an attack of excruciating pain in the left chest, radiating to the left arm. No relief from nitroglycerin which previously was very effective in controlling the anginal attacks. Only slight relief after 3 injections of $\frac{1}{4}$ grain morphia. Marked sweating, pallor, collapse. After 24 hours pain changed to an ache which persisted for a few days and then disappeared. Heart not enlarged on physical examination and x-ray. Rate 120; definite gallop rhythm and pulsus alternans. At times showed 2:1 heart block with temporary rate of 60. Râles developed at both bases. Wassermann negative. B.P. 160/92 June 1, 1923, 95/75 June 27, 1923. This gradually rose and for 4 years remained around 125/85. Temperature around 100°F. for 11 days. E.K.G. showed inversion of the T waves and diminution in amplitude of the curves as compared to those taken before the attack. Patient gradually recovered after the most violent illness we have witnessed. He was in satisfactory health, doing active work as a general practitioner for almost 5 years, except for an attack of what seemed to be a pulmonary infarct 3 years ago. He had no angina since the first attack of coronary thrombosis but died April 7, 1928 after a second attack of coronary thrombosis. It is interesting that the first attack developed while under treatment for angina, and there was no method of foretelling that this would occur. It is also interesting that with the maintained low blood pressure, angina did not return.

Case 41. Fig. 49. F. M. Male, 43. Patient was previously very well. It was definitely known that he had never had dyspnea or angina on effort. 2 days before admission March 23, 1924, he felt an uncomfortable pressure under the sternum and pain at the apex, radiating to the left arm; vomited, perspired and became pale. Lasted 10 hours; leaving him very weak. Heart slightly enlarged; sounds distant, definite gallop rhythm. Transient spell of auricular fibrillation. B.P. 112/84. One week later 94/70. W.B.C. 16,800. Temperature 100°F. for 2 days. E.K.G. showed suggestive high take-off in T 1, becoming inverted. Patient made a very satisfactory recovery and has been carrying on his work for the past 4 years. He developed permanent auricular fibrillation about 2 years after the attack, and is now under constant digitalis therapy. This is a typical case, which showed at first transient auricular fibrillation, later becoming permanent.

Case 42. Fig. 36. R. K. Male, 49. Previous angina for several months. The day before he was seen at his home June 22, 1924, he was taken with severe pain in the center of his chest; he tried to walk it off. After 6 hours he became cold and clammy; slight relief from nitroglycerin

for half an hour. Vomited, pain grew worse, and after 24 hours he was left with a soreness in his chest. Heart was rapid, rate 127; 1st sound of fair quality; gallop rhythm. Râles in both lungs. The following day partial heart-block developed with halving of the rate at times. June 24, 1924 pericardial friction was heard and lasted for 1 week. W.B.C. 31,000. Urine, specific gravity 1038, large trace of albumin, sugar present. Numerous R.B.C., W.B.C. and brown granular casts in the sediment. Ten days later urine was practically negative. Temperature 100° to 101°F. for 10 days. B.P. 170/130 in 1923; 160/110, June 23, 1924, in the morning; 140/108, June 23, 1924, in the evening; 90/70 June 24, 1924; 124/86, October 3, 1924. E.K.G. taken 4 months after the attack showed curves of very low amplitude. At this time patient was ambulatory, free from all symptoms, although the 1st heart sound was entirely inaudible at the apex. Patient has remained well for about $3\frac{1}{2}$ years. This was a typical case, showing a marked permanent fall in the blood pressure with excellent recovery, accompanying the disappearance of angina.

Case 43. A. O. Female, 68. Patient had a good deal of indigestion and attacks of pain in the abdomen, thought to be due to gall-stones. Two weeks before admission November 11, 1915, had severe cutting pain in the epigastrium with pain over the heart. This gradually diminished in 3 days. It radiated to the back and arms and the fingers of the right hand were stiff for a day. One week ago diarrhea. On the day of admission, tightness in the throat, dyspnea, cough and bloody sputum. Heart regular; sounds faint. Numerous moist râles through both lungs; leathery friction rub over right chest. B.P. 148/84. A few minutes after the first examination patient suddenly became cyanotic, gave a few gasps and died. Autopsy showed thrombosis of descending branch of the left coronary artery, and rupture of infarcted portion of the left ventricle, with hemopericardium. This was a typical case, and it is interesting that the diagnosis was broncho-pneumonia before the patient entered the hospital.

Case 44. T. B. Male, 39. For 1 year typical anginal attacks, and intermittent claudication. 5 days before admission, February 4, 1916 felt poorly and later had sudden pain in the epigastrium, with slight radiation to the nipples. Cough, raising blood streaked mucus and vomited frequently. Patient rather stuporous, cyanotic, and complained of pain in the epigastrium. Respiration 34. Pulse 150. Heart: Apex not seen or felt; sounds distant and weak. Many moist râles over left lower lobe. Tender, indefinite mass extending from right costal margin to umbilicus. Definite

icterus of sclerae. Upper abdomen was very rigid. Patient seemed to be in extreme shock. W.B.C. 21,400. Temperature 102°F. B.P. 92/80. Blood Wassermann negative. He was thought to have an acute surgical condition, and was etherized; the differential diagnosis being acute pancreatitis, gall-bladder disease or perforated gastric ulcer. The spasm in the upper abdomen and the tender mass in the right upper quadrant were very striking. Patient died on the operating table. Autopsy showed an extensive infarct of the left ventricle, large mural thrombus; descending branch of left coronary almost obliterated. Nothing of importance in the abdomen except marked congestion of the liver. This is an extremely important case, which in recent years could easily be recognized. In view of the existing knowledge in 1916, exploration was justifiable. It illustrates how coronary thrombosis may present many of the cardinal features of acute surgical conditions of the upper abdomen.

Case 45. S. H. Male, 76. 8 months ago an attack of unconsciousness; since then an occasional dizzy spell. On morning of admission, August 18, 1918 suddenly became unconscious. Cheynes-Stokes breathing; heart sounds very distant; soft systolic murmur; occasional extra-systole. Few râles at left base. Neck stiff; bilateral Kernig and Babinski; B.P. 115/60; W.B.C. 14,800. Urine scant, showed a trace of albumin and numerous granular casts. Temperature 99°F. for 4 days, then rose to 104°F. Spinal fluid normal. Patient remained in coma and died August 23, 1925. Autopsy showed marked coronary thrombosis, infarct and mural thrombus of left ventricle; there was also chronic vascular nephritis. In this case the details of the history were unobtainable, but apparently it was a silent infarct occurring in a patient with extensive vascular and renal disease.

Case 46. E. C. Female, 41. Nine months before was ill for 6 weeks with some kind of kidney trouble. Three weeks before admission January 8, 1921 dyspnea on exertion developed. Two weeks later distressing orthopnea. Heart not enlarged; apex impulse not made out; 1st sound quite indistinct; action regular, no murmurs. B.P. 160/120. Few râles at the bases of the lungs; liver markedly enlarged. Patient grew worse, dyspnea strikingly out of proportion to the other findings. Later there was some choking and oppression under the sternum. Signs at the right base suggested broncho-pneumonia, but 1 liter of fluid was removed by thoracentesis. Distinct leucocytosis. Temperature 100° to 102°F. Patient grew worse, had occasional hemoptysis and died January 22, 1921. Autopsy showed thrombosis of the descending branch of the left coronary artery;

left ventricular mural thrombus; extensive infarction of the wall; thrombosis of the pulmonary artery and several infarctions of the lung and right kidney. This was essentially a painless instance of coronary thrombosis, but the diagnosis was suspected because of the striking discrepancy between the marked dyspnea and the other features.

Case 47. A. P. Female, 65. In very good health until 2 months before admission August 13, 1921, when she was awakened one night with a feeling of constriction in the chest. Since then palpitation and marked dyspnea. For one month confined to bed with dyspnea and swelling of the legs. Heart enlarged; action grossly irregular. Soft systolic murmur present. Numerous moist râles in the lungs. Marked peripheral edema. B.P. 105/55. W.B.C. 15,600. Temperature 100°F. Patient was irrational, showed Cheynes-Stokes breathing. Heart became regular and the day after admission she collapsed and died. Autopsy showed an old infarct of right ventricle and a recent infarction in the left ventricle, with small mural thrombus in right ventricle. Kidneys showed chronic nephritis. This was a fairly typical case in which was the added factor of chronic nephritis.

Case 48. E. L. C. Male, 64. For 10 years was known to have high blood pressure. Patient came into the hospital in extreme collapse and no history could be obtained. Marked pallor, extreme dyspnea and slight cyanosis. Skin cold, moist and clammy. Numerous bubbling râles throughout lungs. Heart sounds rapid, regular and distant. Patient died in 25 minutes. Autopsy showed marked coronary sclerosis and infarction of left ventricle at the apex. There was slight bilateral hydrothorax. This illustrates the type of problem that arises where no previous history can be obtained. Diagnosis may rest on the appearance of shock and distant heart sounds.

Case 49. M. C. Female, 61. Diabetes for 2 years. Controlled well by diet until the last 6 months, during which time she lost 30 pounds in weight, developed weakness and thirst. Three days before admission September 23, 1924, went to bed because of extreme weakness and then became semicomatose. She seemed to have diabetic coma, although she could be aroused to answer questions. Heart not remarkable. Occasionally heart rate would fall from 90 to 45 probably due to 2:1 heart block. B.P. 115/70. W.B.C. 21,000. Urine showed 2 per cent sugar, positive for diacetic acid, and numerous hyalin and granular casts. Blood sugar 0.51 per cent. Blood CO_2 18 vols. per cent. She received insulin treatment, total of 120

units in 24 hours. The next day she seemed to be out of coma and suddenly died. Autopsy showed infarct of posterior portion of left ventricle with rupture and hemopericardium. Right coronary was markedly sclerosed and was occluded by a recent thrombus the left not particularly so. Left hemothorax. This case is remarkable in that patient had both profound diabetic acidosis and coronary thrombosis, and for a while it was feared that the patient had died of insulin shock. It is also of note that the left ventricle was infarcted although the right coronary was the one involved.

Case 50. Fig. 76. S. W. Male, 52. Mild diabetes for 4 years. One year ago sharp attack of pain in epigastrium, radiating to left scapula, lasting half an hour. One month before admission, October 19, 1922, awakened with very severe pain similar to the attack a year ago. Patient screamed, vomited, became short of breath. Pain lasted for 2 days and 5 days later became breathless in trying to walk and a constant precordial distress returned. Heart enlarged; sounds of poor quality, frequent premature beats; definite gallop rhythm; pulsus alternans; râles in both bases. Liver dullness 5 cm. below costal margin. B.P. 95/65. Temperature 100°F. E.K.G. showed an occasional nodal beat and slurring of the Q-R-S complex. Patient slowly improved for 2 weeks; no further anginal attacks occurred but a month later dyspnea grew worse and edema developed. He showed evidence of marked congestive failure. Venesection gave considerable temporary relief. He gradually failed and died December 17, 1922. Autopsy showed an old organized thrombus of descending branch of the left coronary artery; aneurysmal formation in left ventricle; fibrous pericarditis; extensive infarction both lungs with large thrombus in pulmonary arteries; thrombo-phlebitis of common iliac and femoral veins. This case was unusual because of the extensive thromboses of various blood vessels.

Case 51. Fig. 20. P. W. D. Male, 50. For 5 years had angina pectoris. Two weeks before admission March 27, 1925, after dinner he had a very severe attack. At first he tried to walk it off, but his physician gave him morphia hypodermically, and even etherized him and controlled the pain. Heart sounds distant; no murmurs; apex impulse not made out. B.P. 100/60. E.K.G. showed suggestive changes in T 3. Patient recovered and has done very well for the past 3 years. This is a fairly typical case, the pain was so severe that the physician considered it wise to administer ether.

Case 52. Fig. 69. J. N. T. Male, 49. For 2 months had attacks of indigestion which felt like "gas on the stomach which couldn't be raised."

On the day before admission April 2, 1925, during usual exertion was taken with a violent pain in the chest, broke out in a cold sweat, and had marked dyspnea. He had to lie on the floor. Pain in severe form lasted 5 hours but persisted to some extent. Apex impulse not seen or felt. Heart not enlarged, sounds almost inaudible. B.P. 110/50. Gallop rhythm was later heard. W.B.C. 12,100. Temperature 101°F. for 4 days. Pulse around 120. E.K.G. showed high take-off in T 2 and interesting changes in the T wave during the illness. Patient recovered very satisfactorily, and has maintained a low blood pressure and gallop rhythm ever since ($2\frac{1}{2}$ years). This is a fairly typical case, with good recovery and maintained low blood pressure.

Case 53. C. E. H. Female, 65. Diabetes for 10 years. Hypertension for a few years. Cerebral accident 1 year ago. For 2 weeks before admission, May 10, 1925 palpitation and marked dyspnea. Patient entered the hospital somewhat drowsy. Heart regular, sounds distant, no murmurs. B.P. 140/82 (2 years previously 224/110). W.B.C. 11,400; polymorphonuclears 90 per cent. Urine showed a large trace of albumin, specific gravity 1030, sediment showed numerous fine granular casts. Marked glycosuria. Blood sugar 0.53 per cent. Blood CO_2 27 vols per cent. Temperature 101°F. Patient grew gradually worse and died May 15, 1925. Autopsy showed left ventricular mural thrombus, almost complete occlusion of descending branch of left coronary artery, partial occlusion of the circumflex branch, and renal arterio-sclerosis. There was a definite slight purulent pericarditis in which streptococci were found. In this case, as far as our data went, the attack was painless and the picture was masked by the element of acidosis, which was probably diabetic, and by the urinary findings indicating renal disease.

Case 54. Fig. 19. S. D. Female, 45. Patient was always well; had no evidence of previous angina pectoris, when 11 days before admission, May 7, 1925 had a sudden gripping pain in the heart, extending to both arms and the left shoulder. This lasted 20 hours, and left her with marked weakness and sense of oppression in the chest. Heart slightly enlarged, regular, no murdurs; apex impulse feeble. B.P. 90/75. 6 months later 144/94. W.B.C. 7,900, May 7, 1925. E.K.G. showed marked inversion of T 1 which gradually disappeared. The complexes became quite small. Patient improved very satisfactorily, became ambulatory, and remained fairly well for $2\frac{1}{2}$ years, having occasional attacks of pains in the arms on exertion. This was a typical case, in which it was definitely known the attack of coronary thrombosis was not preceded by angina pectoris.

Case 55. Fig. 9. F. H. C. Male, 57. Had rheumatic fever at the age of 8. For 1 year anginal attacks. Four months ago fell from a wagon, was unconscious and later had ache in chest. Three months ago violent attack of vice-like pain in the chest and dyspnea lasting 3 hours. Returned to work as a fireman in 10 days. Increasing dyspnea since. Six days before admission, November 1, 1924, awoke from sleep with the worst attack he ever had. He had a sense of choking and boring in his heart and thought he was going to die. Had to walk the floor to seek relief. Pain persisted for 6 days. Heart was distinctly enlarged, gallop rhythm. B.P. 180 systolic in October 1924; 150/92, November 1, 1924; 130/70, December 7, 1924. W.B.C. 12,900 (74 per cent neutrophiles). Renal function tests normal. Temperature 100°F. for 3 days. Pulse rate 100 to 115. Transient attack of auricular vibrillation on the first day, and on November 23, 1924, fibrillation became permanent. E.K.G. showed a high take-off in T 3 and marked Q 3. During the early days he developed evidence of congestive failure; chest was tapped for hydrothorax. On November 9, 1924, he became desperately sick and was very strikingly helped by bleeding (800 cc. removed). He had a slow convalescence but was discharged in a fairly satisfactory condition. On June 30, 1925 had sudden left hemiplegia and unconsciousness, and developed marked congestive failure again and Cheynes-Stokes breathing; again became ambulatory after a month's treatment. On February 15, 1926, he dropped dead while walking the street. This case illustrates the inception of congestive heart failure following an attack of coronary thrombosis. The hemiplegia was probably due to an embolus dislodged from a left ventricular mural thrombus.

Case 56. Fig. 24. S. F. Female, 52. Very marked family history of vascular disease, the father, mother and 3 brothers having died of shock. For 6 years had hypertension complaining of palpitation and of slight dyspnea. One year frequent angiñal attacks. May 9, 1925 had a severe attack of chest pain radiating to both shoulders and arms. Felt nauseated and fainted. Terrific pain lasted ½ hour. She was left weak with a dull ache in her chest. Entered the hospital June 9, 1925. Heart slightly enlarged, no murmurs, frequent ventricular extra-systoles. B.P. 240/110 June 9, 1925 (160 systolic, May 15, 1925). E.K.G. showed high take-off in T 3 and a sharp Q 3. Patient recovered and the anginal attacks persisted on effort. Patient was still ambulatory 2½ years later. This case had been carefully observed for many years; she had long standing hypertension, later developed angina, went through an attack of coronary thrombosis, and blood pressure which temporarily fell returned to a higher level, and with it the angina returned.

Case 57. H. R. Male, 80. Mother died at 93. Father killed accidentally at 80. One year ago had three fainting spells and lost consciousness. For 7 months dyspnea on climbing stairs. For several weeks some pain in his chest. 10 days before admission, August 24, 1925, dyspnea became acute; had convulsions that night for 30 minutes, with some mental confusion. Heart impulse could not be made out—sounds distant; action regular; no murmurs. B.P. 108/76. W.B.C. 21,000 (neutrophiles 92 per cent). Patient did poorly and had collapsing spell and died about an hour later, August 27, 1925. Autopsy showed fresh infarct of left ventricle, mural thrombus, and occlusion of descending branch of left coronary artery. This patient had a painless infarction, the onset being indicated by sudden dyspnea. It is interesting that this patient, who was the oldest in our series, had such a good family history from the point of view of longevity.

Case 58. Fig. 41. J. P. M. Male, 47. For 8 months typical attacks of angina pectoris on effort, later coming even at rest. While in the hospital with this condition he had an attack of pain in the right upper quadrant, radiating to the chest, followed by blood-tinged sputum. Pallor, sweating and marked asthenia. On August 25, 1925 apex impulse not seen or felt; first sound distinctly diminished. B.P. 132/76 before the attack, August 9, 1925; after the attack 90/60 August 30, 1925. E.K.G. showed no striking changes. W.B.C. 15,000. Temperature 99° to 100°F. and pulse 90 to 120 after the attack. Râles numerous in both lungs. Wassermann reaction strongly positive. Urine showed moderate number of casts; phthalein test 66 per cent. Pain subsided; patient died in state of collapse, August 31, 1925. Autopsy showed syphilic aortitis, acute infarction of left ventricular wall, mural thrombus, marked narrowing or coronary orifices, although the branches themselves were not particularly sclerosed or thrombosed. This was one of the few syphilitic cases. It was known here that before the attack of infarction the blood pressure was not elevated. Also it illustrates that infarction of the heart may occur without a true thrombosis of the vessel.

Case 59. C. W. J. Male, 61. For 4 months had increasing dyspnea and palpitation, but no chest pain. Gradually developed evidence of marked congestive heart failure. This improved very strikingly under treatment. On September 9, 1925, two days before his second admission to the hospital, he had slight pain in the right chest. Physical examination showed enlarged heart; regular rhythm with occasional premature beats, systolic and diastolic murmurs at the base. B.P. 198/125 August 5, 1925;

152/110 September 11, 1925; 130/90 October 4, 1925. W.B.C. 7,200. Temperature 100°F. Pulse 100, on September 11, 1925. He developed congestive heart failure and died on October 10, 1925. Heart showed a sclerotic type of aortic stenosis, fresh infarct at the apex of the left ventricle, mural thrombi in both ventricles. Coronary vessels, though tortuous, were patent. Infarction in right lung. This is another instance of infarction of the ventricles without actual occlusion of the coronaries. There were also thrombi in both ventricles.

Case 60. L. G. Male, 42. Diabetes for 6 years; satisfactorily controlled by diet. Seven weeks ago had an attack of "acute indigestion" consisting of vise-like pain in the epigastrium. Many attacks of angina on effort since then. On the morning of admission, September 24, 1925, awoke with pain in the left epigastrium. While walking to work he vomited and became quite weak. He remained ambulatory though pain continued. Heart slightly enlarged, regular, no murmurs. Sounds very distant. He appeared very sick and in a shocked anxious state. B.P. 70/66. Liver distinctly enlarged and tender. W.B.C. 16,000 (82 per cent neutrophiles) September 24, 1925. Next day W.B.C. 32,600. Temperature 100.4°F. Pulse 100. Patient died in 24 hours. It is interesting that although death occurred in one day, the patient walked to work during the early hours of the attack.

Case 61. Fig. 66. B. P. S. Male, 65. Typhoid fever in 1919. For 5 years anginal attacks consisting of a "clutch in the sternum" on effort. Nine hours before admission February 26, 1926, he was taken with a severe pain behind the sternum radiating down the left arm; not relieved by nitroglycerin or morphine. This awoke him from sleep and lasted for 15 hours. He vomited twice and had some dyspnea. Heart somewhat enlarged, regular, no murmurs, sounds of fair quality. B.P. 130/68, August 13, 1919; 226/120, February 20, 1926; 190/118, 12 hours after attack; next morning, 180/108; that afternoon 160/90; following morning 120/80. It continued at about 120/90. On March 1, 1926, a pericardial friction was heard, in the 5th space near the sternum and lasted 2 days. Leucocytosis present. Temperature normal the first day, then ranged about 102° to 101°F. for 6 days, with a secondary rise to 100°F. for 7 days during the third week. E.K.G. showed typical high take-off in T 1 and T 2 and a marked Q 3. It is interesting that the electrocardiograms taken about 12 hours after the attack did not show the characteristic changes in the T wave which appeared later. Patient made a satisfactory recovery, has remained ambulatory but

still complains of anginal attacks (2 years later) and the blood pressure has returned to about the level before the onset. This patient was seen developing hypertension after typhoid fever; the blood pressure gradually fell over the course of 48 hours. It is significant that the first temperature was normal and the characteristic changes in the E. K. G. did not appear till the second day.

Case 62. Fig. 5. H. G. B. Male, 53. For 3 months slight dyspnea and palpitation. One week before admission. April 15, 1926, he caught cold, had aches and cough. Four days later developed marked dyspnea and nocturnal orthopnea, and sharp aching pains across chest extending into right arm in the form of attacks relieved by belching. Heart was enlarged; apex impulse difficult to locate; action rapid and regular; a definite pericardial friction was present. Temperature 99.5°F. by mouth. No rectal temperature taken. Pulse 130. E.K.G. showed low take-off in T 2 and T 3. Patient was walking around the ward before complete examination could be made and died instantly on day of entry. This was a fairly typical case. In the electrocardiograms the T waves came off below rather than above the isoelectric line. The very low mouth temperature is not at all uncommon during the state of shock; a rectal temperature however, probably would have shown some fever.

Case 63. Fig. 27. E. O. G. Male, 75. Slight increase in dyspnea for 6 months. Twelve days before admission, March 22, 1926 had uncomfortable oppression in the chest; in bed only 4 days. One week later suddenly grew worse with dyspnea, epigastric distress and pallor. Heart enlarged, regular, moderately loud apical systolic murmur. B.P. 142/56, March 22, 1926; 96/70, 5 hours before he died. W.B.C. 7,900. Temperature 99° to 100°F. Pulse 90 to 100. E.K.G. were not very striking on first examination but later showed quite characteristic changes in the T wave. Patient gradually grew worse and died April 5, 1926. Autopsy showed occlusion of the circumflex branch of the left coronary artery; infarction of the left ventricle at the apex and extending over posterior surface and a mural thrombus. There was no pericarditis, the infarction involving the internal portion rather than the external portion of the myocardium. In this case, the electrocardiograms were distinctly helpful for the diagnosis was somewhat obscure without them.

Case 64. Fig. 78. J. W. Male, 57. For several years increasing dyspnea and cough. No chest pain. Entered hospital, March 29, 1926 for

treatment of congestive heart failure. Heart was enlarged; moderately loud systolic murmur at apex and base; asthmatic type of râles throughout chest. Liver enlarged; moderate edema of the legs. B.P. 140/110. W.B.C. 14,000. Urine showed considerable albumin, casts and red blood cells. Phthalein test 50 per cent. Temperature normal for first month. During his stay he developed pain in the left upper quadrant, thought to be due to infarct of the spleen. E.K.G. showed slight delayed conduction before digitalis was started. Patient gradually worse and died, May 10, 1926, with a picture of myocardial insufficiency. Autopsy showed 1000 cc. pericardial fluid with some fibrin. This was probably due to pericarditis as there was no ascites or hydrothorax. There was a recent infarction involving both ventricles and septum; an old healed infarct in the base of the left ventricle, anterior surface. Coronary vessels were patent and not particularly sclerosed. Mural thrombi in both ventricles. Infarcts of lungs, spleen and kidney. This is another instance where the element of infarction of the heart is masked by the previous long standing congestive heart failure. It also illustrates the typical changes that occur in the ventricles despite the fact that the coronary arteries remain patent.

Case 65. Fig. 53. S. N. Female, 49. Four weeks ago an attack of epigastric pain on walking, lasting a few minutes. Since then frequent similar attacks and recently they came without effort. On the day before admission, June 24, 1926, had a very severe attack lasting 30 minutes. Heart slightly enlarged; apex impulse not made out; no murmurs, sounds distant. Liver slightly enlarged and tender. B.P. 185/110, June 21, 1926; 145/85, June 24, 1926; 115/70, July 5, 1926. W.B.C. 7,700. Temperature 99.2°F. for first 6 days. E.K.G. showed striking changes in T 2 and T 3, also a marked Q 3. Patient did very well, but because the pain was in the epigastrium the question of gallstones came up. Intravenous cholecystograms were negative. Patient recovered and 1½ years later has angina attacks, blood pressure having risen to about 170/90. This is a good instance of a case with mild symptoms suggesting gall-bladder disease. E.K.G.'s were very helpful.

Case 66. Fig. 58. C. N. P. Male, 56. Palpitation for 2 years. During past 4 months several attacks of severe chest pain requiring morphia. Last one began about 2 weeks before admission, July 26, 1926, lasting almost a day. Heart distinctly enlarged, gallop rhythm; scratchy sound heard during diastole. B.P. 105/70, July 26, 1926; 75/40, August 8, 1926. W.B.C. 15,000. Temperature 100°F. first 2 days; normal thereafter.

E.K.G. showed notching of the Q-R-S complexes and slight dipping in T 1. Substernal discomfort continued most of the time. While the patient was apparently doing fairly well, he suddenly had a collapse and died in a few minutes August 17, 1926. Autopsy showed thrombosis of the left coronary artery, with a recent infarction in the left ventricle and part of the septum. Also there was a left ventricular mural thrombus, and in the posterior part of the left ventricle, a large area of fibrosis, probably an old infarct. This is a fairly typical case in which death was sudden although no rupture occurred. It is in such instances that one may speculate that the death was due to sudden ventricular fibrillation.

Case 67. Fig. 35. J. N. I. Male, 42. For 5 weeks typical anginal attacks. Three days before admission, September 30, 1926, had severe attack lasting 6 hours. Two days later another attack lasting 12 hours during which he received 6 doses of morphia. With this there was slight dyspnea and cough. The pain gradually tapered off into a dull ache in the chest. Heart not enlarged; apex not seen or felt; distinct gallop rhythm was heard; no murmurs. There was marked cyanosis. B.P. 180/100, August 1926; 135/75, September 30, 1926; 110/90, October 3, 1926. W.B.C. 13,500 (81 per cent neutrophiles). Phthalein 60 per cent October 26, 1926. Temperature 102° to 103°F. per rectum, first 7 days. Pulse 140 on admission, 100 to 120 during next 7 days. E.K.G. showed progressive changes in T 1 that were fairly characteristic. Patient gradually improved, was doing well, when on November 5, 1926, after learning of the death of a dear friend, he had a typical attack of violent acute pulmonary edema. He again improved and was discharged as ambulatory. 4 months later he died suddenly. This was a typical case and it is interesting that 5 weeks after the attack an emotional upset produced pulmonary edema.

Case 68. P. A. D. Female, 76. Two years slight dyspnea. Two months ago an acute illness diagnosed bilateral pneumonia. Three days before admission, June 27, 1926 developed nausea, vomiting, and went into coma. Glycosuria was found. Heart regular; sounds of fair quality; systolic murmur all over precordium. B.P. 130/70. It was known that she previously had had hypertension. W.B.C. 33,900 (93 per cent neutrophiles). Urine showed no albumin, 2.2 per cent sugar and strongly positive for diacetic acid. Temperature 98°F. rectally, pulse 115. Blood sugar 0.88 per cent. Patient was treated for diabetic coma receiving 85 units of insulin in a few hours, but died on the day of admission. Autopsy showed practically occlusion of the descending branch of the left coronary artery.

No mural thrombi or pericarditis. There was pulmonary edema. This case was interesting in that both marked diabetic acidosis and coronary thrombosis were present at the same time. It is also significant that even the rectal temperature can be normal, as was proved in this case.

Case 69. Fig. 44. C. U. M. Male, 68. Patient was previously well, never having had any symptoms indicating angina pectoris. Two days before admission, February 6, 1926, after a hard day's work in the practice of medicine, ploughing through the snow to make his calls, he was taken with a severe clutching pain under the sternum, radiating to both nipples and both arms. Later vomited. During the first 24 hours while pain was still present, heart rate was 62. During the next 4 days rate was from 90 to 100. Heart was distinctly enlarged; when the rate had risen there was a definite gallop rhythm and friction rub. B.P. 145/90, December 1925; 136/80, February 5, 1926; 124/76, February 6, 1926; 94/62, February 7, 1926. W.B.C. 13,200 (78 per cent neutrophiles). Temperature 100° to 101°F. for the first several days. E.K.G. showed curves with characteristic changes in T 1 and Q-R-S waves were low in amplitude. Patient made a splendid recovery and has been practising medicine for 2 years since the attack. This case is rather typical except that during the first 24 hours the pulse rate was unusually slow. The attack here came after a strenuous and fatiguing effort.

Case 70. F. S. T. Male, 60. Increase in dyspnea since 1916. Also had 2 attacks of unconsciousness. He developed the evidences of ordinary mild congestive heart failure in 1923; and was in the hospital several times at yearly intervals, each time improving under treatment. Heart was always enlarged and showed a systolic murmur. B.P. at all times was around 125 systolic and 90 diastolic. He finally came in January 14, 1926, and gradually failed, with evidence of myocardial insufficiency. Died February 20, 1926. E.K.G. showed a variety of disturbances in the rhythm at one time or another. Transient auricular fibrillation, premature auricular beats and nodal rhythm were observed at different times. Autopsy showed adherent pericardium over the site of healed infarct; the descending branch of the left coronary was a solid cord for 2.5 cm., although patent below this. There was a right auricular thrombus and infarct of the lung. There was an old infarct involving the apex of the left ventricle and lower portion of the septum. Part of the ventricular wall was 2 mm. in thickness. This is an example of silent coronary thrombosis occurring in a patient with congestive heart failure.

Case 71. H. A. Male, 60. One month before examination, June 23, 1922, he had a sudden severe pain under the sternum while lifting a heavy box. Pain lasted 8 hours. Previous to this he was always well. He developed temperature of 101°F. and friction rub at that time. Heart enlarged, regular, sounds very distant, S 1 almost inaudible. No murmurs. B.P. 134/80. E.K.G. showed sharp inversion of T 1. Patient did very well and had no chest pain whatever for $3\frac{1}{2}$ years. In October, 1925 he had a second attack of chest pain, collapse and died in 8 hours. This was a typical instance coming on during severe effort with very satisfactory recovery for $3\frac{1}{2}$ years.

Case 72. Fig. 2. H. A. Male, 58. Father died suddenly of heart disease at 54. One sister died suddenly of shock at 51. For 6 months before he was seen in consultation, February 14, 1926, he had pain under the sternum on walking. On February 26, 1926, while in bed he was taken with severe pain in both elbows, later radiating to the chest, had a lot of gas and vomited for 4 days. The distress in his chest lasted for several days. Temperature 99.8°F. Heart was regular, 1st sound diminished in intensity, no murmurs were heard, although 4 months later a definite systolic murmur was present. B.P. 130/90. Patient gradually improved and was in very good health for 2 years when he suddenly died February, 1928. Two months after the attack E.K.G. was not particularly significant. The interesting feature in this case is that the pain started and remained localized in the elbows for several hours.

Case 73. S. B. Male, 59. Patient was a very strong, hard working man. For 6 months pain in the chest on effort. Two days before he was seen in his home, May 14, 1926, while lifting a heavy weight, he suffered a terrific pain in the mid-sternum. This continued. He later vomited and developed edema of the lungs. When examined he was unconscious; heart sounds were absolutely inaudible; lungs were full of moist râles. Patient was pulseless and no blood pressure reading could be obtained. Temperature 96°F. by mouth and 99.6°F. by rectum. Patient did not regain consciousness and died the same day. This was a typical case coming in a powerful muscular man during a very strenuous exertion. Unconsciousness and pulmonary edema developed rapidly and death was not instantaneous, occurring 2 days after the onset.

Case 74. G. E. B. Male, 63. Two years before he was seen at his home, May 31, 1923, a posterior gastro-enterostomy was done for duodenal

ulcer, since when he has felt well, gained weight, and worked hard. On the morning of examination he had severe pain in his chest and went into shock. Heart rate fell to 52, received ½ grain morphine; pain continued. Heart was enlarged, action slow and regular, first sound of very good quality. Liver was slightly enlarged. Few râles heard at both bases. B.P. 142/94. Temperature 100° to 101°F. for a few days. On June 2, 1923, definite pericardial friction rub was heard. Later developed dyspnea and orthopnea, Cheynes-Stokes breathing, and became irrational. On June 10, 1923, developed hemiplegia and died. This was a very typical case, cerebral embolus occurring from mural thrombus on the tenth day. It is interesting that during the 1st 24 hours the pulse rate was very slow.

Case 75. A. B. Male, 46. Patient considered himself well and sought no medical advice, although on close questioning he admitted having a feeling of congestion in his throat when climbing hills or in cold weather. Eight days before he was seen in his home, May 6, 1927 while walking in the street he was taken with pain under the sternum extending into both arms. He broke out into a cold sweat and became very weak. After 12 hours the pain turned into a mild distress. Heart sounds were very distant especially the 1st sound. No murmurs. B.P. 130/80. Temperature 100.8°F. Pulse 90. Developed transient auricular fibrillation; an uncomfortable feeling in the chest persisted. He seemed to be doing fairly well, however, when on May 9, 1927, he suddenly died. Neither the patient nor the physician knew that he ever had anything wrong with him previously, although careful questioning brought out a definite history of angina pectoris of 6 months duration.

Case 76. P. F. C. Male, 56. Patient was previously in very good health, never having suffered any chest distress on effort before. Three days before he was seen at his home October 18, 1923, he was suddenly taken with severe pain in the upper chest radiating to the left axilla. When seen his heart was very rapid, rate 167; heart easily slowed temporarily by vagal pressure. Tachycardia was considered to be due to auricular flutter. Urine contained 1 per cent sugar. Temperature 99.4°, 99.6°, 100.6°, 102°F. the first 4 days respectively. Pulse was 68 and 72 the first 2 days of the attack; later around 100 except for the transient tachycardia. Patient gradually recovered and has done well the past 4½ years. The interesting feature of this case is that the patient developed what seemed to be paroxysmal auricular flutter on the third day after the onset.

Case 77. A. D. Male, 64. Was a mild diabetic for 10 years. Three years ago a similar but milder attack than the present one. For 6 weeks definite anginal attacks on effort. Thirty-four hours before he was seen at his home, January 28, 1927, after great excitement and running around, that resulted from fire breaking out in his home, he was taken with a terrific pressure in his chest which felt like "2 tons of bricks" hitting him. The pain radiated to both arms. This feeling continued for several days. He also stated that his heart felt as if it was spreading or bursting. Heart slightly enlarged, sounds very distant and slight systolic murmur was heard. B.P. 102/80, January 28, 1927; 80/78, February 2, 1927. Temperature 101° rectally. A few days later heart was suddenly found to be very rapid, around 155. The rhythm although essentially regular had slight irregularities at times. Vagal pressure produced no change. Patient had previously been given large doses of digitalis. The exact interpretation of this arrhythmia was difficult; the various possibilities were auricular flutter, auricular fibrillation, or the rare condition of complete heart block with rapid ventricular rate as result of digitalis intoxication. The condition seemed desperate. Next day the possibility of a ventricular tachycardia arose. Quinidine sulphate (0.3 gram) was given intravenously which slowed the heart from 155 to 120. The rate became rapid again an hour later. Quinidine was given by mouth after this in increasing doses, never more than 0.6 gram t.i.d. No effect was produced. Intravenous ouabaine 0.5 mgm. was given as a remote hope; no change resulted. Patient died, February 10, 1927. We now know definitely that the disturbance in the mechanism of the heart was ventricular tachycardia, and in the light of our experience with case no. 133, we might have stopped the rapidity and thereby possibly saved this patient's life if we had continued quinidine in increasing doses. This case illustrates the importance of the bedside diagnosis of ventricular tachycardia which is now quite well established (63).

Case 78. C. D. Male, 63. 3 years before he had an attack of severe pain in the lower sternum and epigastrium, became pulseless and almost died. This was called acute indigestion. He was very well after this until 4 days before he was seen at his home, July 15, 1920, when while lifting a row-boat he had a terrific attack of pain in the upper abdomen, broke out into a cold sweat, and seemed to be in collapse. During the next few days the abdomen was somewhat distended and no fecal material could be obtained by repeated enemas. Some gas, however, was expelled. A surgeon was called because of the possibility of acute intestinal obstruction. He was not satisfied with the diagnosis, bringing up the possibility of a mesenteric

thrombosis or some chest condition. Heart was slightly enlarged, first sound definitely faint, slight basal systolic murmur. Râles at both bases; slight dullness at right base (possibly due to high liver). Liver extended 2 finger breadths below the costal margin. B. P. 90/68. Temperature 98.8°F. by mouth; 100.6°F. rectally. Pulse 116. Diagnosis of coronary thrombosis made rather than acute surgical abdomen. Patient recovered satisfactorily and 2 months later died suddenly while in bed. This case illustrates the importance of differentiating coronary thrombosis from acute surgical condition of the abdomen.

Case 79. W. D. Male, 65. For 2 years there was pain in the upper sternum radiating to the throat with a choking sensation, coming at first on effort and later on rest. Four days before he was seen in his home, April 16, 1926, he had the same sort of spell "only a thousand times worse." The pain continued. Heart slightly enlarged; 1st sound markedly diminished in intensity. B.P. 240/120 (1924); 110/78, April 16, 1926. Temperature 99.8° and later was 101.2°F. Heart rate 88 at first and later 106. On April 19, 1926, a definite pericardial friction rub was heard; developed Cheynes-Stokes breathing and evidence of circulatory insufficiency. He gradually grew worse and died April 21, 1926. This is a typical instance of coronary thrombosis occurring in a man with previous hypertension and angina pectoris.

Case 80. Fig. 21. J. E. Male, 59. For 4 months typical anginal spells on effort. Seven days before he was seen as an ambulatory patient, February 25, 1926, the same sort of pain began that he previously had but did not let up. It continued for about a week. It did not prevent his walking around although it was rather annoying. No murmurs in the heart, but the sounds were very distant. Heart not rapid. E.K.G. showed a rounded T 2 and a sharply inverted T 3. Patient recovered and except for occasional attacks of anginal pain has remained in fair health for 2 years. In this case it is interesting that the attack of coronary thrombosis developed almost insensibly after a 4 month's interval of angina pectoris. Patient remained ambulatory although the pain which was mild was continuous. E.K.G.'s were very helpful.

Case 81. M. E. Male, 51. Although this patient knew he had hypertension with definitely no evidence pointing to a previous angina pectoris, 14 days before he was seen at his home November 28, 1924, without any previous warning he had a severe clutch in the chest, became ashen in color

and went into collapse. Heart slightly enlarged, sounds very distant, rate 88. B.P. 210/120 (½ hour after onset); 114/70, November 21, 1924. W.B.C. 20,000. Temperature 100.3°F. Pulse 120. Patient was in bed for 6 weeks and made a very satisfactory recovery. He did very well for 1½ years; then began to have dyspnea. B.P. rose to 176/110. In the fall of 1926, at which time E.K.G. showed curves of very low amplitude, he grew gradually worse, having nocturnal orthopnea and dyspnea. He showed gallop rhythm, Cheynes-Stokes breathing and marked evidence of congestive heart failure. There was no chest pain. He died December 27, 1926. This was a typical case in which there was no precedent angina; recovery took place; death occurred 2 years later from congestive heart failure.

Case 82. Fig. 22. J. F. Male, 47. Marked family history of angina pectoris in that his father and a brother died of it. Was well up to 8 weeks before he was seen in the office, December 2, 1925, when he was suddenly taken with severe pain in the chest, radiating to the back and to the throat. The pain lasted 5 days. He was in bed several weeks, and was free from pain after this. Heart distinctly enlarged, action regular, first sound quite faint. B.P. 136/90. E.K.G. taken 2 months after the attack showed changes in T 2 and T 3 that are typical of the late findings in coronary thrombosis. This case illustrates quite well the helpfulness of electrocardiograms in the diagnosis of a previous coronary thrombosis.

Case 83. Fig. 25. S. F. Male, 45. For 7 years there were typical attacks of angina in which the pain radiated to the gums. One week before he was seen in the office, November 9, 1925, as an ambulatory patient he had terrific attack of chest pain, lasting about a day in which he did not get the customary relief from nitroglycerine. Heart not enlarged, action regular, first sound almost inaudible. B.P. 140/80 (November 9, 1925 during anginal pain); 108/78 (3 minutes later after relief from nitroglycerine). E.K.G. showed sharp inversion of T 3. This patient recovered from the attack of coronary thrombosis, although at no time did he go to bed for it, but since then for the past 2 years has had very frequent anginal attacks, sometimes requiring 80 nitroglycerine tablets a day. This case is interesting in that patient recovered although he remained ambulatory throughout.

Case 84. A. G. Male, 53. No previous angina. 8 weeks before he was seen at his home October 30, 1926, he had a terrific attack of pain in the chest and vomited several times. Pain lasted several days, and in the wake of this developed signs of congestive heart failure. Heart slightly enlarged,

sounds diminished in intensity, no murmurs. Liver considerably enlarged; numerous moist râles at both bases and musical asthmatic râles throughout the lungs. B.P. 105/70. He was treated with digitalis and potassium iodide, at one time was quite dyspneic and showed Cheynes-Stokes breathing, but finally improved. In January, 1927, while apparently doing satisfactorily he suddenly died. This was one of the few cases in which there was not only coronary disease, but asthmatic bronchitis.

Case 85. M. G. Male, 43. Sixteen months ago he had attacks of angina pectoris. 3 days before he was seen in his home, April 14, 1927, he had a severe attack of "squeezing" pain in his chest lasting 24 hours. He found it hard to breathe and vomited several times. Heart not enlarged, action regular, rate 94. First sound of good quality, no murmurs. B.P. 180/100 (1925); 116/90 April 14, 1927. Temperature 98°F. Recovered satisfactorily and has been back at work ever since. In this case the previous hypertension disappeared with the attack; it is interesting that the quality of the 1st heart sound was normal, although in most cases it has been found to be faint.

Case 86. Fig. 26. J. G. Male, 46. Both the father and a brother died suddenly at age of 42 of angina pectoris. For 1 month previous to the attack he had anginal spells. Fourteen days before he was seen at his home, August 31, 1925, he had an attack of collapse with severe chest "constriction," broke out in cold perspiration, and vomited. The pain lasted 24 hours, then there was a soreness in the chest. Heart distinctly enlarged, 1st sound very distant. Slight basal systolic murmur. B.P. 110/70, August 31, 1925; 90/79, September 16, 1925; 120/78, March 31, 1927. After a very critical illness patient recovered and has had only occasional mild anginal attacks for the past $2\frac{1}{2}$ years. E.K.G. several months after the attack showed a Q 3 and sharply inverted T 3. This is a fairly typical severe case, with satisfactory recovery. The striking family history of angina pectoris occurring early in life is worthy of note in this case.

Case 87. D. G. Male, 60. For 5 years definite angina pectoris. One-half hour before he was seen in his home, November 5, 1926, he was taken with a terrific attack in which he collapsed. When examined he was cold, semi-conscious, skin was moist, and pulse was barely perceptible. Heart rate 102, sounds almost inaudible. B.P. 80/70. Patient died in 3 hours. This case illustrates the type in which death occurs rapidly in a patient in a state of collapse.

Case 88. S. H. Male, 67. Ten years previously he was known to have had hypertension. For 2½ years he had attacks of "indigestion with belching of gas." 28 hours before being seen at his home, December 7, 1921, while riding in an automobile he had severe pain under the lower sternum, vomited, and collapsed. The pain felt "like a load" in his chest, radiated to the left arm and continued for 2 days. When seen, he was still in a cold sweat. Heart slightly enlarged, first sound absolutely inaudible, no murmurs. B.P. 156/90. Patient gradually recovered after a long illness, returned to work, and 12 months later went through a similar attack and again recovered. He has remained in fair health for the past 6 years, attending to his duties as a merchant. This case illustrates the fact that after recovery from the coronary thrombosis the patient may remain in satisfactory health for many years.

Case 89. Fig. 33. J. H. Male, 58. For 3 years mild anginal symptoms on effort. Five days before he was seen in the office, April 14, 1927, as an ambulatory patient, he had a constant pain under the sternum and belching of gas, lasting 1½ days, not relieved by nitroglycerine. After the 2nd day the pain was entirely gone. The morning after the onset temperature was 100.5°F. and he had transient auricular fibrillation. Heart slightly enlarged. There was a faint systolic murmur at the apex; 1st sound diminished in intensity and there were occasional premature beats. B.P. 166/98 (1925); 134/85, April 14, 1927. E.K.G. were taken before the attack and shortly after the onset, and showed distinct change in the form of the T waves. Patient took it easy only during the 1st two days, yet made a satisfactory recovery. He has been practicing medicine ever since, although he has let up in the amount of work. This was a fairly typical mild case in which the minor changes that took place in the electrocardiograms after the spell as compared to the form of the curves before the attack were both significant and helpful.

Case 90. B. H. Female, 72. Anginal attacks for 3 months. Two weeks before she was seen at her home, April 5, 1926, had a severe attack of constriction of the chest, broke out in a cold perspiration and vomited. The acute pain lasted 2 hours and following this there was soreness in the chest. Heart negative except for a slight systolic murmur. B.P. 220/120 (February, 1926); 100/60, March 26, 1926. Patient developed transient auricular fibrillation. In the course of the next several weeks increasing evidence of congestive heart failure and Cheynes-Stokes breathing developed. She gradually grew worse and died in May, 1926. This is a typical case of coronary thrombosis developing in a hypertensive individual.

Case 91. Fig. 34. J. F. H. Male, 44. For 1 year anginal attacks. Four weeks before being seen in his home, January 11, 1927, he had a terrific attack of "pressure" in his chest extending into both arms; this lasted 24 hours after which there were milder attacks of pain. Heart was enlarged, regular, first sound slightly diminished in intensity; no murmurs. B.P. 160/110, November 8, 1926; 140/104, January 11, 1927. Patient continued to have minor anginal attacks which were decidedly helped while taking euphyllin. He returned to work and in December 1927 had a sudden attack of acute pulmonary edema without pain. He again improved very strikingly as a result of phlebotomy, and now is ambulatory. This case is interesting in that about a year after an attack of coronary thrombosis patient had an attack of acute pulmonary edema without chest pain.

Case 92. H. K. Female, 50. Five years before she had a severe attack of angina pectoris. Since then suffered "compression" in the ensiform region on effort. On the day before she was seen in her home, February 28, 1923, she had a terrific attack and the pain continued. Heart was regular except for an occasional premature beat, when suddenly during the examination the heart rate accelerated to 180; this was considered to be paroxysmal ventricular tachycardia. B.P. before this disturbance occurred was 140/88. Patient died ½ hour later. This case illustrates the possible gravity of the development of ventricular tachycardia in a patient with coronary thrombosis. The treatment of this condition with quinidine has been discussed elsewhere.

Case 93. Fig. 38. F. W. K. Male, 72. For several months had mild anginal symptoms. Six days before he was seen at his home, July 3, 1925, he was taken with a compression of the chest which at first was not very severe, but gradually grew worse in the course of the next few hours; requiring 3 doses of morphia hypodermically. Severe pain lasted 18 hours. Heart not enlarged; first sound faint; no murmurs. Râles were heard at both bases. B.P. 160/95 (June 27, 1925 shortly after the onset): 118/82, July 3, 1925. Temperature 99° to 100°F. for 1st 4 days. Pulse 80 to 90 the first day and 100 to 110 for next 3 days. Patient made a very satisfactory recovery and was well for 2 years. In August, 1927, he had a somewhat similar attack, slightly less severe and again recovered. He is now ambulatory and in fair health. E. K. G. taken October 25, 1927, were not particularly remarkable. This case was very carefully observed through the 2 attacks of coronary thrombosis with an interval of good health lasting 2 years.

Case 94. N. L. Male, 51. Had hypertension for 3 years and angina for 3 months. Four days before he was seen in his home March 1, 1927, he had very severe attack of pain in the center of his chest which continued for $3\frac{1}{2}$ days. Heart slightly enlarged; sounds very faint; frequent premature beats were heard. B.P. 92/55, February 27, 1927; 115/75, March 1, 1927. On the day following the onset the pulse was suddenly found to be 40; this probably was 2:1 heart block. The outcome of this patient is not known.

Case 95. H. L. Male, 56. Two brothers died of coronary thrombosis at the ages of 55 and 62. In 1923 patient was operated on for lymphosarcoma of the small intestine. After this he was in very good health until 2 days before he was seen in his home March 3, 1927, when he was taken with a terrible attack of pain in the chest and collapse while delivering an address. When his doctor reached him, patient was pulseless, unconscious and almost dead. He injected 1 cc. of 1/1000 adrenalin in the arm, and shortly after this, patient revived. When he was seen in his home, heart was not enlarged, regular, rate 104, sounds diminished in intensity, no murmurs. B.P. 120/70, March 2, 1927; 90/50, March 3, 1927. Urine contained 3 per cent sugar. Temperature 97.8°F. by mouth, 101°F. rectally. Pulse 100 to 110. He developed marked dyspnea and Cheynes-Stokes breathing for which he was given caffeine subcutaneously. He improved after this. Glycosuria disappeared without insulin. From March 10, 1927, to March 14, 1927, he had pericardial friction rub. March 12, 1927, he had right hemiplegia and aphasia from which he partially recovered. During the second week he suddenly developed a rapid heart rate of 170 essentially regular with slight changes in the rhythm and varying intensity of the 1st heart sound; vagal pressure produced no effect. He was given increasing doses of quinidine, and on 0.5 gram normal rhythm was restored. This disturbance in the mechanism was considered to be due to ventricular tachycardia. He again improved and was doing very well, when on April 26, 1927, the morning he was expecting to sit up in a chair for the first time he suddenly died. For 2 weeks before this he had received no medication. In this case we have instances of 3 brothers all dying of coronary thrombosis. It also illustrates how easy it is to overlook the fever if the temperature is taken by mouth. Finally, this is a further example of ventricular tachycardia responding to quinidine sulphate.

Case 96. S. L. Female, 67. Asthma for many years. Three days before she was seen at her home February 21, 1926, was taken with a sudden

pain under the sternum, vomiting and collapse. The heart was not enlarged, regular, rate 80, no murmurs, sounds of fair quality. B.P. 120/60 (a few days before systolic pressure was 150). Temperature 99.5°F. Patient developed mental symptoms, became irrational, gradually grew worse and died, February 30, 1926. This is another case that might have been called acute indigestion.

Case 97. M. L. Male, 62. Brother of case no. 95. For several years had mild diabetes; blood pressure over 200 systolic; and for 4 years definite anginal attacks. Thirty-six hours before he was seen June 3, 1923, he suddenly developed marked sternal pressure and terrific edema of the lungs, raising a great deal of pink frothy sputum. Patient was cold semi-conscious and heart sounds were barely audible; rate 116. During the first 2 hours of the attack the systolic blood pressure fell from 170 to 130 and then to 100. Partial heart block was detected on auscultation. He received adrenalin with temporary improvement, but died 6 hours later, June 3, 1923. In this case the marked feature was the sudden onset of pulmonary edema.

Case 98. S. L. L. Male, 65. For 10 years has had hypertension. Three weeks before he was seen in his home December 6, 1924 he had sudden substernal distress, marked dyspnea and vomiting. Two days after the onset he had a pericardial friction rub and later had transient auricular fibrillation. B.P. 150/100, December 6, 1924. He gradually developed signs of congestive heart failure, pitting edema of the legs, Cheynes-Stokes breathing and dyspnea; for a while he improved on digitalis, but then grew worse and died January 5, 1925. This is a very typical case in which congestive heart failure developed and proved fatal.

Case 99. I. M. Male, 52. Mild angina for 2 years. Two weeks before he was seen in his home, May 9, 1925, he had an attack of severe chest pain which lasted for 2 days. Edema of the lungs developed. Examination showed distant heart sounds and a definite pericardial friction. B.P. 160/84 (the reading was 120/70 the day after the attack.) Patient recovered very satisfactorily and has remained fairly well for the past $2\frac{1}{2}$ years. There is nothing unusual in this case.

Case 100. B. M. Male, 47. For 2 years he had attacks of distress in his chest which were suspected of being due to angina pectoris. Two weeks before he was seen in his home, December 9, 1924, he had the same sort of

attack, only a great deal worse. He later raised bloody sputum. On examination heart sounds were almost inaudible. Liver was enlarged and tender; B.P. 96/70. He had two transient attacks of auricular fibrillation. The cough, bloody sputum and dyspnea gradually cleared up, patient recovered and has remained in fairly good health in the past 3 years. The interesting feature in this case is the development of pulmonary edema and hemoptysis. This may have been due to infarct of the lung coming from a right ventricular mural thrombus.

Case 101. E. M. Female, 58. For 6 months repeated anginal attacks. Three days before she was seen at her home, January 5, 1927, she had a very severe attack of compression of the chest which continued for 24 hours. Heart was somewhat enlarged, sounds of good quality, action regular. B.P. 240/140. Temperature 100.4°F. Pulse 98. Ophthalmoscopic examination showed marked retinal arterio-sclerosis. After the pain had subsided she felt fairly comfortable and 5 days after the onset, while apparently well, she suddenly died. This case illustrates very well the rare instance in which blood pressure does not fall.

Case 102. Fig. 43. W. E. M. Male, 55. First attack of angina was 5 weeks before. One week later had a bad attack of pain in the chest lasting 24 hours. When seen, December 23, 1926, the heart was considerably enlarged, regular, rate 100, sounds somewhat distant. B.P. 102/90. At this time patient was ambulatory, at work and feeling slightly weak and apprehensive. E.K.G. showed a typical rounded inverted T 1. Before these tracings were examined it was doubtful whether the attack that occurred one month before was very serious. The diagnosis of coronary thrombosis was greatly aided by the electrocardiograms. Patient kept at his work against advice and on February 11, 1927, he suddenly died. This case illustrates the value of electrocardiography in the diagnosis of a previous recent attack of coronary thrombosis.

Case 103. Fig. 48. C. M. Male, 55. For several months dyspnea on walking. March 1, 1925 he had a severe pain under the sternum radiating to both arms, became ashen and grew very weak. Pain lasted off and on for several days and then he gradually recovered. One month later after he was up and about he had a similar attack. With this he had transient auricular fibrillation. When seen, June, 1925, heart was enlarged, action regular, slight systolic murmur was present. B.P. 190/110, January, 1925; 130/110, April, 1925. Temperature 102°F. during the first attack. Gradu-

ally recovered. Formerly he was very obese, weighing 260 pounds, but on advice he lost 50 pounds. He has an occasional attack of angina now, but has remained in fair health for 2½ years. In this case there were 2 separate episodes of severe chest pain of long duration with collapse, the second coming 1 month after the first. It illustrates the importance of a longer period of rest in bed.

Case 104. Fig. 50. M. M. Male, 44. No previous angina. While at home a few hours before he was seen, October 30, 1926, he suddenly had severe pain in the chest radiating through to the back, up to the neck and down both arms. With this he found it hard to breathe and vomited. Pain lasted about 24 hours. Heart not enlarged, sounds normal in quality, no murmurs. B.P. 102/64. Temperature 100° to 102°F. for 5 days. Pulse 90 to 100. Urine contained slight trace of sugar. For a few days before this illness he had a slightly sore throat. Patient recovered satisfactorily after a long period of rest in bed and has remained in good health for the past year. E.K.G. taken several months after the attack showed a prominent Q 3. This is a fairly typical case in a patient who had no previous angina.

Case 105. Fig. 55. M. O. Male, 49. For 2 months he had mild anginal attacks. Two weeks before he was seen in the office as an ambulatory patient, December 7, 1925, he had a severe attack that awoke him from sleep, which lasted 3 hours. Heart slightly enlarged, sounds very distant, no murmurs, frequent premature beats. B.P. 100/70. E.K.G. showed frequent ventricular extra systoles and complexes of low amplitude. Patient made a satisfactory recovery and has been at work for the past 2 years. This apparently was a mild attack from which the patient recovered without spending more than a few days in bed.

Case 106. Fig. 57. F. P. Male, 54. On careful questioning no previous history of angina could be ascertained, although 7 years before he had a somewhat similar but milder spell for which he was in bed for 2 weeks. One month before he was seen in the office, January 14, 1927, he had severe chest pain which continued for 36 hours. Pain gradually let up but he remained in bed for about 3 weeks. Heart not enlarged, first sound of good quality, no murmurs. B.P. 145/88. E.K.G. taken one month after the attack was essentially normal. The patient continued to do well and has been at work ever since. It is interesting in this case that electrocardiograms one month after the onset of the attack were normal.

Case 107. S. P. Male 44. This patient was previously in excellent health, being able to do strenuous things without chest distress. Seventeen days before he was seen in his home, February 6, 1925, he had terrific feeling of pressure under the ensiform cartilage, became short of breath and very restless. The pain lasted several days. Heart slightly enlarged, regular, with definite gallop rhythm. First sound faint, systolic pressure 140 the first day and during the next few days gradually fell to 95. He developed a pericarditis and transient fibrillation was also noted. Temperature 101°F. the first 3 days, then gradually fell to normal by the end of one week. The patient recovered after 7 weeks of bed treatment, and returned to work. One year after the attack he was still in good health. This was a typical severe case with satisfactory recovery.

Case 108. J. P. Male, 67. This patient was a powerfully built, muscular man. For 4 weeks he had typical anginal attacks on effort. Six hours before seen at his home, May 6, 1927, he had a terrific attack of compression in his chest with the pain radiating down both arms and wrists. He then vomited. Heart not enlarged, regular, first sound muffled, no murmurs. B.P. 135/85. Pain lasted about 12 hours and then there remained an ache in the chest. Patient gradually recovered, became ambulatory and returned to his work. This was a typical case with recovery.

Case 109. S. R. Female, 56. Was apparently in good health until 25 days before being seen in her home, April 14, 1926, when she had a very severe attack of pain in the chest lasting 3 days. She remained in bed and was doing well until 24 hours ago when severe chest pain returned, followed by a collapse. Heart regular, sounds distant, no murmurs. B.P. 180/100, March 20, 1926, the day of the first attack. This gradually fell to 135/80. On April 13, 1926, the readings were 96/40; April 14, 1926, 50/35. Temperature 99.6°F., March 22, 1926; 103.8°F., April 14, 1926. Pulse 100 to 120. Patient seemed to be in a state of shock and died the following day. It is interesting here that as late as 3 weeks after the first pain, while the patient was apparently doing well she went into collapse and died.

Case 110. A. H. R. Male, 63. For 4 years had anginal attacks. Ten hours before he was seen, February 21, 1923, he had terrific pain in his chest and became unconscious. Patient was cold, clammy and in state of severe shock. Heart sounds were almost inaudible, rate 130, grossly irregular. Radial pulse could not be felt and no blood pressure could be obtained. There was Cheynes-Stokes breathing. He was given intravenous strophan-

thin without any beneficial effect, and he died 12 hours later. This case illustrates the type in which unconsciousness develops soon after the onset of the attack.

Case 111. I. S. Male, 59. Had hypertension for several years. In August, 1926, had a right hemiplegia. For past 2 months had anginal attacks, readily relieved by nitroglycerine. Two days before being seen at his home, March 19, 1927, had an attack of more severe chest pain radiating to the left arm which persisted and was not relieved by nitroglycerine. Heart considerably enlarged, sounds were distant, a definite gallop rhythm, no murmurs. Heart rate 110, which occasionally would change to 55, indicating a 2:1 heart block. B.P. 210/110, January 1927; 154/84, March 19, 1927; 190/100, May 8, 1927. Lungs showed evidence of asthmatic bronchitis. Temperature 101.6°F. rectally. Patient gradually recovered and blood pressure rose to the previous high level, and with this anginal attacks returned. This was greatly helped by euphyllin. On August 9, 1927, severe and constant chest pain returned and he died 3 days later. This case showed a partial heart block and blood pressure did not fall to a very low level, and as it became elevated again, a second and fatal attack of chest pain occurred.

Case 112. J. S. Male, 56. For 16 months he had anginal attacks. Twenty-four hours before he was seen in his home, March 3, 1922, he had sudden severe chest pain while in bed. This persisted until 2 hours ago when he became pulseless and cold. Heard sounds almost inaudible, no murmurs, action regular with an occasional loss of an entire beat, indicating partial heart block. B.P. 80/66. Patient did not respond to stimulation and died the following day. There was nothing particularly unusual about this case.

Case 113. Fig. 62. D. S. Male, 67. History of gout and for 1 year had occasional attack of angina pectoris. Seven days before he was seen in his home, February 11, 1926, he had a terrific constriction in his chest and vomited several times. Two days later he had a spell of transient auricular fibrillation. B.P. 228/108, February 11, 1926; 185/90, October 29, 1926. After 2 days the pain let up but kept recurring during the following week. He gradually recovered and has remained in fair health during the past 2 years. E.K.G. taken February 4, 1927, were not remarkable. The previous history of gout in this case is a point of interest.

Case 114. S. S. Male, 54. For 3 weeks there were frequent spells of angina pectoris on slight exertion. One hour before he was seen December 30, 1924, he had a most violent attack of pain in the chest which produced terrible agony. He was thrashing around in bed, literally tearing the skin of his chest, crying out that he wanted to die. Patient was in a cold sweat, no pulse could be felt, heart sounds were almost inaudible, the rate changing from 80 or 90 to 40, and at times there would be complete standstill of the heart for several seconds. Apparently there was intermittent complete heart block. Blood pressure 8 days before this attack was 144/80. Patient died about a half-hour later. In this case the striking thing was the terrific agony that the patient suffered and the heart block that developed.

Case 115. Fig. 65. T. J. S. Male, 46. On July 3, 1925, was suddenly taken with an attack of pain in the chest, perspiration and weakness. Before this he never had chest discomfort but since then his heart has felt "high up in the throat." When seen in the office August 17, 1925, heart was not enlarged, occasional premature beats were heard, slight systolic murmur was present. B.P. 90/60, July 5, 1925; 120/70, August 7, 1925. Two days after the onset, temperature 99.0°F., pulse 110. E.K.G. August 7, 1925, showed a prominent Q 3 and a large inverted V-shaped T 3. Patient did very well, returned to his work as a surgeon and 2 years later, in May, 1927, he fainted at the operating table, and died suddenly half an hour later. This was a very typical case in which electrocardiograms one month after the attack were extremely helpful in the diagnosis.

Case 116. I. S. Male, 65. For 2 weeks he had anginal attacks even at rest. Several hours before he was seen at his home, March 22, 1927, he had a terrific pain in the chest for which his physician administered ether. Heart sounds very distant, no murmurs. Frequent premature beats were heard. Temperature 99.2°F. Pulse 63. Patient gradually recovered and has been back at work this past year. It is interesting in this case that ether was used to relieve the patient of chest pain.

Case 117. I. S. Male, 57. For 4 weeks before he was seen at his home, July 8, 1925, he had violent pain in his chest lasting 24 hours. After this increasing evidence of cardiac decompensation developed. Patient was sent away to the country for a rest; he was permitted to be out of bed during the day although he suffered from orthopnea during the night. He grew worse and returned home. When he was seen, he was in extremis. The heart was enlarged, sounds diminished, action regular. B.P. 112/84 July

8, 1925. Liver was enlarged and tender. Temperature 100°F. Pulse 110. Patient died the same day. In this case congestive heart failure developed in the wake of an attack of coronary thrombosis. It was poor advice to allow this patient to travel and to be out of bed after the attack.

Case 118. F. M. S. Male, 63. Seven years before typical angina developed. Two years ago he had a left cervical sympathectomy with complete relief of the anginal symptoms. Ten weeks before he was seen in his home, April 24, 1926, a sudden attack of chest pain returned while the patient was in bed. The agony was terrible and lasted 3 days. After the pain let up there was temporary improvement but this was followed by signs of cardiac decompensation. Heart sounds were very distant, there was distinct gallop rhythm and pulsus alternans. B.P. 190/116, January 10, 1924; 100/80, February 12, 1926 (directly after the attack): 145/100 April 24, 1926. The day after the attack W.B.C. 21,000, temperature 102°F., pulse 120. Marked dyspnea and orthopnea developed. Cheynes-Stokes breathing was present. After a long illness he died June 5, 1926. It is interesting in this case that although a cervical sympathectomy completely relieved the patient of anginal spells, even on extreme effort, 2 years later violent chest pain accompanied the coronary thrombosis. The finding of pulsus alternans is not at all rare.

Case 119. Fig. 67. C. S. Male, 64. For 10 days there were mild anginal spells. Four hours before he was seen June 11, 1924 he had a terrific pain in the chest radiating into both arms, lasting about 24 hours. Heart not enlarged, first sound fair quality, no murmurs. B.P. 160/95 (before the attack); 140/90, June 11, 1924; 128/80, June 16, 1924. Temperature 99.4°F. Pulse 90. E.K.G. showed slight changes in the T wave which disappeared in the following year. Patient made an excellent recovery and for the past 3½ years has had no chest pain. This is a typical case of moderate severity with excellent recovery.

Case 120. M. T. Male, 67. For past 1½ years attacks of angina, the pain radiating to both arms and into the right ear. Five days before he was seen in his home, March 16, 1927, he began to have attacks that would last 2 to 3 hours, and yesterday a terrific pain began which has continued. Heart was enlarged, sounds were very distant, definite gallop rhythm was present. Temperature 99.8°F. by rectum. Pulse 74. Numerous râles at both bases. Pain finally disappeared when he began to have dyspneic attacks with Cheynes-Stokes breathing. Signs of congestive heart failure

developed and liver became enlarged. He finally died April 20, 1927. Here the interesting features were the premonitory symptoms for several days when the attacks that previously lasted a few minutes began to last a few hours. It is also significant that the pulse rate remained slow for a while after the beginning of the attack of coronary thrombosis.

Case 121. A. L. K. V. Male, 70. For several years he had been taking thyroid gland for myxoedema. Angina pectoris for 3 years. While quiet at home, a few hours before he was seen, May 25, 1923, he had a violent attack of pain in the chest with suffocation and cold perspiration. Twelve hours later a definite pericardial friction rub was heard lasting $1\frac{1}{2}$ days Heart sounds very distant. During the subsequeut days transient auricular fibrillation developed. Temperature 100.2°F. May 25, 1923. He recovered very satisfactorily and after a month in bed went to his country home. During the following week he suddenly developed a hemiplegia and after this gradually grew worse and died August 15, 1923. The significant points here are the development of angina pectoris, and coronary thrombosis in a patient who had been taking thyroid gland for myxoedema. This is not an uncommon occurrence. Furthermore, it is interesting that a cerebral embolus developed as late as 5 weeks after the coronary thrombosis. This indicates that the period of rest in bed should have been longer.

Case 122. R. W. Male 66. On definite questioning there had never been any previous anginal attacks. The day before he was seen, April 11, 1927, he had severe upper abdominal pain and belching of gas. This lasted 4 hours and then he experienced bad vise-like pain in the chest and vomiting which lasted for 2 days. Heart slightly enlarged, sounds diminished in intensity, no murmurs. B.P. 160/100 (July 1926); 98/70, April 10, 1927. Temperature 100°F. Pulse 90. Patient had a very satisfactory recovery and has been at work ever since. This was a case of moderate severity with the pain localized in the upper abdomen for the first few hours. It is also an instance in which the attack of coronary thrombosis was the initial evidence of heart disease.

Case 123. S. W. Female, 60. She was definitely free from any chest distress before this attack. Three hours before she was seen in her home December 29, 1926 had a terrific pain in her chest while in bed, went into collapse, became pulseless and vomited. Heart slightly enlarged, frequent premature beats, no murmurs. Sounds almost inaudible. B.P. 130/85, December 30, 1926; 116/70, January 1, 1927. Temperature 96.6°, 99.6°,

and 100.2°F. by rectum, 6 hours, 12 hours and 22 hours after the onset respectively. Pulse 62 during the first 24 hours and did not rise any higher. Râles were present at both bases. Patient had an uneventful recovery and has remained well for the past year. This case illustrates the slow pulse at the onset, and the gradual development of the fever.

Case 124. E. W. Male, 64. Anginal attacks for 1 year. Five days before he was seen in his home, January 26, 1923 he had a very violent attack of pain in the chest with cold perspiration. Heart slightly enlarged, sounds distant, absolutely irregular in rhythm (next day heart was regular). Râles at both bases. B.P. 130/80, January 26, 1923; 160/80, February 21, 1924. Temperature 99.8°F., pulse 84 during the first day. Patient recovered and during the convalescence a systolic murmur and gallop rhythm were heard. Angina pectoris returned. E.K.G. 2 months after the attack showed an inverted T 1 and curves of low amplitude. This has since become normal. He attended to his business for the last 5 years and died April, 1928. It is interesting here that the abnormalities in the E.K.G. practically entirely disappeared.

Case 125. R. S. W. Male, 58. In August, 1925, he had an attack of pulmonary edema. Since then there was some dyspnea and constriction in the chest on effort. Four days before he was seen in his home February 19, 1926, he had another attack of pulmonary edema associated with marked pain in his chest. On examination he was found to be in extremis, cold and moist, heart sounds barely audible and absolutely irregular. B.P. reading could not be obtained, where previously systolic had been 140. He died a few hours later. This case was typical of a form that has acute pulmonary edema.

Case 126. Fig. 82. S. Z. Male, 50. Previously he was in excellent health. Four hours before he was seen January 11, 1927, he had an attack of chest pain and went into a cold perspiration. Heart showed frequent premature beats. No murmurs, first sound faint. B.P. 110/85 (2 hours after onset): 128/95, two hours later; 145/100, February 9, 1927. Temperature 100°F. E.K.G. showed sharply inverted V-shaped T 3, February 9, 1927. Patient has done well and has been back to work for the past year.

Case 127. M. Z. Female, 68. Two days before seen at her home, April 8, 1923, she had severe epigastric distress and feeling of pressure, and the following day she vomited and had marked constriction of the chest.

Heart showed a loud systolic murmur all over the precordium. B.P. 130/90, April 7, 1923; 80/58, April 8, 1923. Urine contained 0.3 per cent sugar. Temperature 101°F., pulse 100. Patient died April 10, 1923. The only remarkable feature here is the localization of symptoms in the epigastrium during the first day.

Case 128. M. Z. Male, 70. For many years has had frequent gall-stone colic attacks. Thirty-six hours before seen in his home, September 14, 1925, he had sudden severe epigastric pain, vomited several times and went into collapse. He later became unconscious. Heart sounds could not be heard at all. Breath sounds were noisy. B.P. 80/70. Temperature 100°F. by rectum. He gradually failed and died September 15, 1925. Here coronary thrombosis developed in a patient who previously had many attacks of gall-stone colic.

Case 129. A. A. Female, 61. For a year had diabetes, hypertension, albuminuria and mild anginal symptoms. Two days before she was seen at her home, June 2, 1927, she had an attack of pain which began in the chest, radiated to the left arm and produced a terrible feeling of clutching in her throat. Heart grossly irregular (later heart was regular). No murmurs, first sound of fair quality. B.P. systolic 200, May 31, 1927; 140, June 1, 1927; 115, June 2, 1927. Urine showed 1.5 per cent sugar. Temperature 100 to 101°F. by rectum. Patient recovered and has been ambulatory since. This was a very typical case.

Case 130. D. W. Female, 66. Diabetes 15 years; hypertension 2 years; angina pectoris 1 year; repeated gall-stone colic several years. Two days before she was seen in her home February 11, 1926, patient stated she had an attack of chest pain which was entirely different from anything she had ever experienced. It continued for $1\frac{1}{2}$ days and she vomited frequently. Heart slightly enlarged, 1st sound of good quality, slight systolic murmur at apex and base. B.P. 200/100, in 1924; 178/92, February 11, 1926; 200/100, May 10, 1926. Temperature 99.4°F. Pulse 110. Patient recovered; when she was again ambulatory the systolic murmur was louder and the anginal attacks recurred. In this case there was no great fall in the blood pressure.

Case 131. M. L. Female, 39. For one year mild anginal attacks. Twelve days before she was seen at her home, January 8, 1925, she had a severe attack of chest pain radiating down both arms. Pain lasted $\frac{1}{2}$

hour and disappeared. After this she was up and about, and 5 days later a second attack occurred lasting 2 hours. Two days later she had a third attack and with this there was marked pulmonary edema. She vomited several times and gradually improved and was again allowed to be out of bed. Two days ago began to have pain in the left leg and later in the right leg. Both legs became cold and then discolored. Heart regular. No murmurs, marked gallop rhythm. B.P. 96/55, January 3, 1925. Pulse varied from 140 to 100. There was dark dry gangrene and greenish discoloration of both legs up to the mid-thighs. Patient died January 17, 1925. This patient was the youngest woman in the entire series. She obviously had an embolus involving both iliac arteries, which probably came from a left ventricular mural thrombus. It was unwise to ever allow the patient to be out of bed after the first attack. It is interesting that there were three different spells of chest pain several days apart before the embolus occurred.

Case 132. Fig. 11. F. S. C. Male, 62. Eight weeks before he was seen in the office, November 2, 1921, as an ambulatory patient he had an attack of severe chest pain with collapse. Heart regular, sounds very faint, especially the first sound at the apex. B.P. 135/85. E.K.G. showed curves of very low amplitude and the characteristic dip in T 1. This patient recovered satisfactorily, remained well, but how he has done in recent years is unknown. There is nothing unusual in this case.

Case 133. Fig. 61. A. R. Male, 53. Patient was very strong and in good health until 3 hours before he was seen in his home, March 23, 1927, when he had a most agonizing pain in the chest radiating into both arms. Two hours later he vomited. Heart sounds extremely faint, gallop rhythm was present. B.P. 158/110, 3 hours after the attack; 120/92, March 25, 1927; 96/76, March 28, 1927; 128/72, May 17, 1927. W.B.C., 12,000 to 14,000 (neutrophiles 77 per cent). Temperature 100° to 102°F. for 4 weeks. During the first few days the mouth temperature ranged between 98° and 99°F. while the rectal temperature varied from 100° to 102°F. This patient ran a very desperate course; several times it was thought that he was going to die. He had numerous complications. He had transient auricular fibrillation, small embolus in the foot and a paroxysm of ventricular tachycardia which was very well controlled by quinidine sulphate. The details of the treatment of this complication was discussed in the early portion of this paper. E.K.G. showed various changes fairly typical of coronary thrombosis. Patient finally recovered and has since become

ambulatory. In this case the early fever would have been missed entirely if the rectal temperature had not been taken. The most important feature here was the life-saving value of quinidine.

Case 134. Fig. 74. S. U. Female, 55. Anginal attacks for 5 years. 7 days before admission to the hospital, December 29, 1926, had a very severe attack of constriction in the chest with nausea and vomiting. Heart essentially negative except the apex impulse could not be made out. B.P. 250/120, December 29, 1926. While in the hospital she had another severe attack of chest pain, January 4, 1927. B.P. fell to 120/75 and within 5 days gradually rose to 225/120. She developed transient auricular fibrillation, showed leucocytosis, transient glycosuria, and slight fever. E.K.G. showed changes in the T wave at this time. She finally recovered and became ambulatory. In this case the main features of the attack were observed while the patient was in the hospital. B.P. fell markedly but returned to the previous high level.

Case 135. Fig. 63. W. S. Male, 69. Had rheumatic fever as a boy. Mild anginal symptoms for 1 year. Seven days before admission to the hospital, February 2, 1927, he had severe constriction of the chest, radiating to both arms, lasting several hours. Pain kept recurring for a few days in a milder form until 3 days ago when he had a very bad attack. Heart sounds distant, slight systolic murmur was heard, action grossly irregular. E.K.G. showed auricular fibrillation. Liver was considerably enlarged. B.P. 160/70, January 1922; 190/90, January 30, 1927; 130/70, February 2, 1927. W.B.C. 26,500 (neutrophiles 70 per cent). Temperature 99° to 100°F. Patient gradually grew worse and died with evidence of congestive heart failure. This patient was seen 5 years before this last illness and on clinical examination was considered to have persistent auricular fibrillation, although no E.K.G. was taken at this time. Autopsy showed almost complete occlusion of the left coronary artery, fresh infarction of the left ventricle, and a mural thrombus. This case is interesting because he probably had persistent auricular fibrillation for years before he had coronary thrombosis, and in this sense was the single exception to the general rule that chronic fibrillators do not develop coronary thrombosis.

Case 136. Fig. 32. G. H. Male, 56. Angina for 2 years. Fifteen hours before admission to the hospital, December 31, 1926 had a terrific pain in the epigastrium. Several hours later severe pain in the right loin. A few hours after this pain developed in the right leg. Seven days before

this he had an uncomfortable constriction in his chest which continued for some hours for which he did not go to bed. In the hospital he was in a state of shock; definite pericardial friction developed. B.P. 200 systolic in 1919; 130/95, December 31, 1926; 110/90, January 1, 1927; 98/78, January 7, 1927. W.B.C. 14,900. Leucocytosis persisted for 1 week. Pulse 160 and later 100 to 120. Temperature 100° to 102°F. E.K.G. showed curves of low amplitude. About this time developed paroxysmal ventricular tachycardia which was controlled by quinidine. He developed gangrene of the right leg for which amputation was performed. He survived the operation but died a few days later, January 13, 1927. Autopsy showed thrombosis of the descending branch of the left coronary artery, left ventricular mural thrombus, infarct of the kidney and embolus in the right popliteal artery. This case is interesting because of the embolic phenomenon for which amputation of the leg was performed, and because the ventricular tachycardia was eliminated by quinidine.

Case 137. Fig. 70. C. T. Female, 47. Diabetes 10 years. Angina 8 years. Six days before admission to the hospital, January 16, 1927, she began having continuous pain in the chest, radiating to the left arm, and marked prostration. Heart sounds very distant, almost inaudible. B.P. 130/60, December 14, 1925; 100/80, January 16, 1927; 110/70, February 7, 1927. W.B.C. 22,900. Leucocytosis persisted for 1 week. Urine showed a good deal of sugar. Temperature 100° to 101° for 17 days. Pulse 100 to 110 for 10 days. Patient had slight acidosis with the diabetes for which insulin was given. She had a good many pains and cramps in her legs. E.K.G. showed minor changes in the T waves; at one time there was 2:1 heart block. She gradually improved, became ambulatory. Seven months later, August 18, 1927 died at home. This was a typical case developing in a patient with long standing diabetes.

Case 138. Fig. 54. M. N. Female, 72. Dizziness for 1 year. Slight edema of the legs for a few months. Seven days before entering hospital May 3, 1921, she had a weak spell followed by pain in the chest. Examination showed a pericardial friction rub; heart sounds were faint; there was a moderately loud systolic murmur. B.P. 200/100 in 1920; 160/85, May 3, 1921; 140/80, May 7, 1921. W.B.C. 14,600. Temperature 101°F., pulse 110 to 130. E.K.G. showed typical high take-off in T 2 and T 3. At times 2:1 heart block occurred. Patient was apparently doing satisfactorily when on May 10, 1921 she went into sudden collapse and was dead in 2 minutes. Autopsy showed thrombosis of descending branch of the left

coronary and rupture of the left ventricle. This is a typical case in which rupture of the heart occurred 14 days after the onset.

Case 139. Fig. 59. J. W. R. Male, 60. Had typical angina pectoris for 9 years. Five days before admission to the hospital, June 1, 1927, he began to have continuous pain in the chest not relieved by nitroglycerine. Pain lasted 12 hours and then disappeared. Two days later pain returned and lasted for 48 hours. Since then there was no severe pain but some discomfort in the chest. Heart showed a gallop rhythm and slight systolic murmur and distant sounds. B.P. 138/96, June 1, 1927; 98/72, June 6, 1927. W.B.C. 7,400. Temperature 100°F., June 1, 1927. Pulse 90. There was at times partial heart block. E.K.G. showed typical high take-off of T 2 and T 3, the curves finally becoming sharply inverted. Patient was doing well when 6 weeks after the onset he suddenly grew worse and died July 7, 1927. It is interesting here that the W.B.C. was normal at the onset despite slight fever.

Case 140. Fig. 4. R. M. B. Male, 52. Had angina for 2 months. Twenty-four hours before entering the hospital May 3, 1927, chest pain began and persisted. With this there was a moderate state of shock. Heart showed no murmurs. Sounds were fair in quality. B.P. 125/80, May 3, 1927; 95/50, May 15, 1927. W.B.C. 24,000 (86 per cent neutrophiles). Leucocytosis persisted for 72 hours. Temperature 100°F. for 7 days. Pulse 100 to 120. Blood Wassermann strongly positive. E.K.G. showed a suspiciously inverted T 1 which became upright. Patient was critically sick for several days, gradually improved without anti-luetic treatment and made a very satisfactory recovery. This is one of the few cases of coronary thrombosis that had a positive Wassermann yet a satisfactory recovery occurred without anti-luetic treatment.

Case 141. Fig. 32. Male, 55. Had hypertension for 2 years. Three days before entering hospital, April 30, 1927, while dancing he was taken with abdominal pain and gas. Four hours later he had constriction in the chest and dyspnea. The chest discomfort was severe and persistent. Heart sounds were distant; there was a definite gallop rhythm. B.P. 180/120, in 1923; 206/130, in July, 1926; 178/130, 20 hours after the attack. Temperature 100°F. by rectum. Patient gradually grew worse. Several times the heart was found to be rapid at a rate of 170. This was due to ventricular tachycardia; the rapidity was readily controlled by quinidine. E.K.G. showed typical high take-off in T 1 and T 2. Marked dyspnea and cyanosis

developed for which he was placed in an oxygen tent. This helped the cyanosis and breathing. He grew worse, however, and become semi-conscious. On May 2, 1927, he developed paralysis of the left arm, probably as a result of cerebral embolus. He gradually failed and died on May 7, 1927. Autopsy showed typical findings. There was left coronary occlusion, left ventricular mural thrombus, ruptured heart and hemopericardium. This case was typical in all respects.

Case 142. Fig. 60. L. R. Female, 62. Angina for 4 years. Ten days before entering hospital May 23, 1927, continuous pain developed in the chest and marked weakness. Heart showed a slight systolic murmur and first sound was of good quality. B.P. 140/90, May 23, 1927; 100/70, May 29, 1927. W.B.C. 11,000. Temperature 100°F. Pulse 90. E.K.G. showed typical sharp inversion in T 2 and T 3. The continuous pain let up but attacks of angina returned. This was greatly helped by euphyllin. Patient gradually improved and has returned to work as a house-maid. There was nothing unusual in this case.

Case 143. Fig. 18. E. R. Female, 58. Angina for 1 year. Entered hospital February 19, 1927 complaining of some indigestion as well as chest pain on effort. It was decided to get x-rays of the gall-bladder, and during the intravenous administration of the iodine dye March 16, 1927, she was taken with severe and persistent chest pain unlike anything she had ever had. The following day she had a W.B.C. of 12,600. Temperature rose and remained between 100° to 101° for 7 days. Heart rate became elevated to 100 to 110 for several days. Heart which previously was essentially negative then showed a gallop rhythm. B.P. 290/120, 1925; 220/130, February 19, 1927; 160/100, March 18, 1927. E.K.G. showed definite changes in the T waves of all leads after the attack as compared to those before the attack. Patient gradually improved and remained free of anginal attacks, although previously the attacks were coming while the patient was in bed. She has since returned to her work as a school teacher. The interesting feature here is the development of coronary thrombosis as the result of intravenous cholecystography. (We have since seen two other instances of this complication.)

Case 144. Fig. 79. A. C. W. Female, 65. Increasing dyspnea for 6 years. Nine days before entry to the hospital, July 3, 1927, she suddenly lost the power of the right arm. Two days later this was much better. Six days ago pain in the right leg followed by numbness and inability to

move it. The day before admission severe pain in right lower chest. Heart negative except for gallop rhythm. B.P. 145/80. W.B.C. 14,600. Temperature 100°F. E.K.G. showed a prominent Q 3 and a rounded T 3. Patient gradually grew worse and died July 7, 1927. Autopsy showed infarct of the left ventricle with a mural thrombus. There was embolism and thrombosis in the right femoral artery. The clinical diagnosis was made in this case despite the absence of chest pain because of the suspicious electrocardiograms and the gallop rhythm.

Case 145. Fig. 56. B. H. O. Male, 40. Was previously in excellent health. Eight hours before admission to the hospital on the surgical service, June 8, 1921, had severe cramp-like pain in the epigastrium. Five hours later this became terrific so that he received ½ grain morphia subcutaneously; vomited once. When first seen he presented a picture of acute surgical abdomen with marked tenderness and board-like rigidity in the upper abdomen. Even after the morphine he was still suffering from severe pain in the pit of the stomach. Complete physical examination was otherwise negative except that associated with the second heard sound there was a doubtful faint scratching murmur. On having the patient sit up and bend forward this scratching sound was more distinct. B.P. 130/70. W.B.C. 15,400. Temperature at that time was normal. The patient was a physician and thought he had ruptured gastric ulcer. The surgeon who saw him was not satisfied with the diagnosis, although many features pointed to acute surgical emergency. E.K.G.'s at that time were considered normal, but now one can detect that the T wave in Lead I arose from a high level. It was decided to delay operation. The next morning a well marked to-and-fro pericardial friction was heard. The pain rose to the chest on this day and then gradually disappeared; patient made a very satisfactory recovery. He has remained in good health for the past 6½ years. This case is a striking example which illustrates the importance of keeping in mind coronary thrombosis as a possible explanation of symptoms and findings that might otherwise point to upper abdominal surgical emergency.

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THE THERAPEUTIC VALUE OF RADIATION

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I. INTRODUCTION

The object of this review is to examine the claims for the therapeutic use of radiation in medicine. The term "radiation" is limited to that emitted by the sun, the mercury vapour quartz lamp, the carbon arc and other so-called generators of "ultra-violet" radiation in use at the present day. The subject of x-ray therapy has recently been covered in an exhaustive review, by Warren (1) and is not included in this study. The subject of diathermy is also omitted.

To review the literature on the subject of radiation therapy is no easy task. The reviewer is faced with a large literature concerning the use of radiation in the treatment of almost every known disease, and a literature so prolific at the present time that to keep pace with it is an almost impossible task.

The discovery of the value of ultra-violet radiation in the cure of certain diseases has, in the past few years, let in a flood of popular

enthusiasm. This enthusiasm runs ahead of scientific knowledge, and threatens to destroy the value of the treatment by indiscriminate use.

At the present time, the value of radiation treatment is discredited by some, and over-emphasized by others. There is, however, another and more thoughtful group, who realise that our limitations are set by lack of scientific knowledge, who refuse to be carried away by undue enthusiasm, or depressed by apparent failure, and who realise that the claims made must be accepted or rejected only on the basis of exact scientific research.

It is encouraging that workers in this field are alive today to the necessity for more research into the fundamental aspects of the effects of radiation on the organism. The discoveries of recent years have done something to pierce the gloom of mystery; it is to be expected that those of the years to come will do much to raise the whole subject from the realm of magic to that of fact.

II. HISTORICAL SKETCH

One of the earliest papers on the subject of the biological effect of solar radiations is that of an Englishman, Home in 1820 (2).

Home's work is of great interest, since he proved by experiment a differentiation between the "light" and "heat" rays of sunlight. He relates in this paper how he was interested to ascertain the function of pigment in the skin of the negro. He evidently felt it likely to prove a protective mechanism against the sun's rays. When he found, however, that black surfaces absorbed heat, and raised the temperature several degrees he "gave the matter up in despair." Two years later he saw "a silver fish" that appeared to have received a sunburn through water, and on a travel to the West Indies he received a sunburn himself "through a pair of thin linen trowsers."

These two observations made him think that sunburn was due "to a mixture of light and heat," and he investigated this in a series of simple experiments. In one of these he exposed the backs of both his hands to sunlight, one covered with a black cloth and the other left uncovered. He tested the temperature of the skin of both hands at intervals of ten minutes and observed two things: that the higher skin temperature was recorded on the covered hand, but that this hand did not become sunburned whilst the other did. He concluded

that the power of the sun to scorch the skin "is destroyed when applied to a black surface, although the absolute heat, in consequence of the absorption of the rays is greater."

This work of Home's apparently provoked little comment at the time. It was introduced into the Danish and German literature by Rasch, who in 1926 (3) made graceful allusion to it in an address to British Dermatologists. Finsen made the same discovery, and, according to Rasch, was at the time unacquainted with Home's work.

In 1823 Colhoun (4) of Philadelphia published a short paper giving some results of experiments on the sensibility of the face to light.

In 1829 Davy (5) confirmed, in the main, the experiments of Home. Davy's experiments are of interest for he took a step towards finding out the rôle of ultra-violet radiation in the production of pigmentation. He found, at any rate, that erythema and pigmentation were not caused by radiations in the visible spectrum. He was probably one of the earliest to experiment with isolated radiations. He says

> My experiments relative to the cause of the change of colour produced in the skin by the sun's rays . . . . tend . . . . to prove that the effect is produced solely by the uncompounded rays. I have exposed, for more than two hours, and that repeatedly, the delicate skin of the under part of the forearm to the solar spectrum, and I have concentrated the different coloured rays of the spectrum by means of a lens on the skin, but without occasioning either erythema or discolouration.

In 1859 Charcot (6) expressed the opinion that the "chemical" rays caused erythema solare, and that a similar erythema could be caused by exposure to artificial sources of light.

In 1877 Downes and Blunt (7) produced the first definite evidence that ultra-violet radiation excited a lethal action upon bacteria. See also Arloing (8), D'Arsonval and Charrin (9).

In 1890 Palm (10) in a classical paper correlated, from a geographical survey, the incidence of rickets with a lack of sunlight.

III. GENERAL CRITICISMS OF PAPERS DEALING WITH THE CLINICAL USE OF RADIATION THERAPY

Certain general criticisms can be made after an exhaustive survey of papers dealing with the use of radiation therapy in the treatment of disease.

1. *Treated cases are usually uncontrolled by untreated cases,* and for this reason the value of the reported results is vitiated. This is especially true in certain diseases with a tendency to spontaneous recovery, and many such have been treated by radiation.

It may of course be argued that if a remedy is known to be specific or if the results obtained with it would warrant it to be the treatment of choice, one is not justified, on ethical grounds, in withholding it. Against this, it may be stated, that in probably only one disease, namely rickets, is radiation *known* to have a specific action, and that in very few diseases, possibly only in lupus vulgaris and bone and glandular tuberculosis, are the clinical results good enough to warrant radiation as the treatment of choice. With these possible exceptions, it would appear that the withholding of treatment from groups of control cases, would not, in this stage of uncertain knowledge, be fraught with bad results for the patients. If clinical studies are to be of scientific value therefore, they must be adequately controlled.

The value of a well-controlled, statistically analysed, clinical study of the value of radiation therapy such as that of Mackay (11) cannot be overestimated. In the clinical field many more such studies are needed. Mackay's results (to be discussed in more detail later) are iconoclastic, since her findings as to the value of the radiations used are negative. They are, for this reason, the more valuable, and should, if given the consideration they deserve, do something to stem the tide of popular enthusiasm.

2. *The use of radiation therapy, as a last resort, in intractable cases.* One commonly finds, especially in studies of radiation in the treatment of skin diseases, that radiation therapy has apparently achieved a cure after the use of all other known remedies. The criticism here is that the cure may be "post hoc sed non propter hoc," since it is impossible to assess the value of any one of a number of forms of treatment used in the treatment of the same case.

3. *Lack of information or unreliable information with regard to the source of light used.* The writer has been surprised, on reading papers by several authors on the subject of the clinical value of radiation, to find that the source of light used is not even mentioned, although the cases treated by it are described in detail. In other papers it may be given a casual mention, but with no information as to voltage, ampèrage, or, if a carbon arc lamp is used, a description of the carbons.

In certain cases, where the source of light is mentioned, unreliable information may be given as to the radiations it emits. Claims, for example, have recently been made for the value of light from an ordinary electric bulb in the treatment of certain conditions, on the assertion that the analysis of sunlight and of light from an ordinary electric bulb are practically identical. This statement is untrue (since the ordinary electric light emits practically no ultra-violet radiation) and therefore misleading.

4. *The tendency to attribute all observed results to radiations in the ultra-violet.* Radiations from almost any kind of therapeutic lamp include a range of rays extending from the ultra-violet, through the visible, to the far infra-red regions of the spectrum. Ultra-violet radiations have certain well-known biological effects, about which more is known than is known about the action of other rays. There is, apparently for this reason, a tendency to disregard the possible effects of visible and infra-red radiation, and to attribute all effects to radiations in the ultra-violet. It is, at any rate illogical, to attribute the whole effect to a few radiations when many are being used. It is possible that one of the future developments in radiation therapy will be the use of selected and isolated radiations. We know, for example that the radiations effective in the treatment of rickets are limited to a very narrow band in the ultra-violet. Also the writer[1] has shown that this band of radiation is more effective alone, than when given in conjunction with an isolated band of radiation in the near infra-red.

5. *Empiricism in the measurement of dosage.* The usual method of measuring dosage is time of exposure, and distance from the source of light. The erythema dose for the individual patient is usually taken as the unit of dosage, and this is only a rough index of the tolerance of the individual to radiations in the ultra-violet. It is furthermore, as we have shown in the section on skin diseases, an extremely variable factor.

These are certain chemical methods of measuring ultra-violet intensity in therapeutic units—the zinc sulphide method (Clark (12)) and the acetone methylene blue method (Webster, Hill and Eidenow (13)). These should be more widely used in clinical work, for they give an indication of the intensity of the source of light in the ultra-violet,

[1] Luce Clausen—in the press.

and make it a simple matter to detect deterioration in the output of the lamp.

With increased knowledge of the biological effects of radiation it may prove necessary to make measurements more exact than this rough, empirical determination of the reaction of the skin of the patient to radiations in the ultra-violet region of the spectrum; measurements that would define limits of wave-length, the spectral distribution of the rays, and the total energy value of the radiations received.

Finsen (82, 84) made the following statement with regard to actinic rays: "I believe implicitly that in the future, use will be made of this new therapeutic agent, and the proof experiment once made, it will be easy to carry it out practically under the form of light baths; and lastly to determine whether they are to be blue or violet, the variations in their strength and duration, and whether natural or artificial." His prophecy with regard to the use of light baths has been fulfilled. We have yet to see the last statement, which prophesies the use of filtered and measured radiation, fulfilled also.

IV. RICKETS

Clark (14) refers to the work on rickets as "the first definite experimental evidence of metabolic change in the animal body brought about by sunlight." The evidence she refers to is that of Huldchinsky (15), Hess and Unger (16), Hess and Gutman (18), Shipley, Park and Powers, McCollum and Simmonds (99, 76).

Since this review of Clark's was published, an exhaustive review on the Etiology of Rickets was brought out by Park in 1923 (20). This review covers all the early literature on the subject of the influence of radiant energy in the prevention and cure of rickets published at the time the review was written.

Laurens (22) in a more recent review on the physiological effects of radiation has covered a great deal of the work on the effects of radiation in rickets, and the experimental work on irradiated foods. The reader is also referred to the section on rickets in a report by the British Medical Research Council (145).

It is entirely unnecessary to go over ground that has been so well covered by these authors, and the reader is referred to them (14, 20, 22, 145) for an exhaustive bibliography, a critical survey of the litera-

ture quoted, and many ideas, which in view of recent developments, would appear to have been prophetic.

It is the purpose of this review to show how the story of the relationship of light to rickets has developed, especially along experimental lines, in the past few years, and has led to the isolation of a substance capable of photo-chemical reaction which we have reason to believe is specific in the prevention and cure of the disease. In reviewing the subject, the author has confined herself to the work of pioneers in the field, and has not attempted a complete bibliography, in order to quote work which will tell the complete story in its main facts, and to avoid side issues.

Clinical

The early clinical and experimental observations on the subject are described by Park (20, pp. 125–126), beginning with the classical paper of Palm (10) in 1890.

Huldchinsky (15) in 1919 reported the first accurate information on the cure of rickets by treatment with the mercury vapour quartz lamp. He demonstrated radiographic evidence of the deposition of lime salts in bone under the action of the radiations used, and to him belongs credit for a great clinical discovery, which was later developed along experimental lines.

Hess and Unger (17) claim to be the first to attempt to cure rickets with ultra-violet radiation, but their first attempt (19) failed; they quote the cases of 5 children with rickets treated with radiations from a mercury vapour quartz lamp, twenty minutes daily to the entire body over a period of three months till their bodies became tanned; they say, "this therapy . . . did not lead to a definite improvement in the rickets, nor did it benefit their general condition. Violet ray treatment cannot be considered the equivalent of heliotherapy, but the fact that rickets is exceptional in the arctic region, where there is lack of sunlight for the greater part of the year, is a strong argument against its predominant influence." In later papers these authors attribute their failure to the lack of x-ray evidence on these five cases. This explanation is not completely satisfactory, for it was evident, by the fact of tanning, that these children received ultra-violet radiation; in the light of present day knowledge one would have expected

curative changes to be apparent even to the naked eye. It should be borne in mind, however, that at the time this paper was published, the prevailing idea, in the minds of these investigators, was to regard rickets as a disease due to a food deficiency. Also early changes in bone indicative of cure were not generally recognized. In 1921 Hess (21) in an address before the Harvey Society still regarded rickets as primarily a dietetic disorder, but lack of sunlight as an important contributory influence.

In later papers Hess and Unger (23, 16, 17) report successful clinical results in the cure of rickets in infants by the use of a mercury vapour quartz lamp, and by exposures to sunlight. This work was controlled by x-ray examination of bone. They noted (16), in one case, calcification taking place during treatment in *both* wrists, when only one had been exposed, and saw in this "evidence that the action of the rays is systemic and not local." This was an important observation and has since been abundantly confirmed. It was followed by a series of clinical papers on the value of radiation therapy by Hess and his co-workers (24, 25, 26, 27, 28). They correlated the seasonal incidence of rickets, with the seasonal variation in the intensity of ultra-violet in the solar spectrum (29, 30).

Experimental

The recent pioneers in the experimental field are Hume and Smith, Rosenheim and Webster, Hess and his co-workers, Steenbock and Black, and Bills.

Special consideration must be given to the early experimental work of Hume and Smith. These workers investigated the effect of light on rats suffering from a deficiency of vitamin A, and their results proved to be of fundamental importance. For though the interpretation of the experiments given by these authors was not correct, the experiments themselves were so admirably carried out that they formed the starting-point of important lines of investigation for other workers. One sees from the work of these authors the value of the careful experiment, and the accurate observation, at a time when a correct interpretation may not be forthcoming.

In discussing the work of Hume and Smith one must bear in mind that at the time the experiments were carried out, the bias of opinion

amongst British investigators was in favor of the identity of an anti-rachitic factor with the so-called fat-soluble A Vitamin, present in cod liver oil and known to be specific for rickets. Hume and Smith conducted their experiments shortly after their return from Vienna, where they were co-workers with Chick, MacKay and Dalyell, in an investigation (under the joint auspices of the British Medical Research Council and the Lister Institute), into the cause of rickets at Pirquet's clinic. The results of this investigation were published by the Medical Research Council in one of their Special Reports (31). These workers had been impressed with the value of radiation therapy in the treatment of rickets in infants, but had not accepted the experimental evidence of McCollum (32) as to the existence of an anti-rachitic vitamin as distinct from vitamin A. It was perfectly logical therefore that they should expect to obtain results by the irradiation of animals fed on a diet deficient, as they thought, in vitamin A only. Their first experiment (33) showed that the radiated animals "developed the typical symptoms of vitamin A deficiency with greater severity and greater rapidity than did the control animals;" at the same time they found that radiation produced a most striking effect in promoting growth. Their explanation of this was an interaction between light and vitamin A for the growth of rats, without any synthesis of the vitamin, since xerophthalmia was not delayed in its appearance. They regarded light as either an economizer of vitamin A, or a liberator of a stored reserve. Still confident that "vitamin A" was the food factor concerned in the cure of rickets, they conclude by saying "The existing experimental evidence does not therefore exclude the possibility that the interplay (i.e., *between growth and light*[2]) in growth and rickets is the same, and the very existence of an interplay in both cases heightens the possibility that the two vitamin factors may be identical or nearly allied."

This experiment formed the main starting point of the work of Steenbock and Nelson (38). These workers were impressed with the careful experimental technique of Hume and Smith and the growth response of their rats to radiation, but dissatisfied with their explanation, which presented "the paradoxical position that light liberates vitamin

[2] The italics are mine.

A for growth but not for the prevention of the ophthalmias." Steenbock and Nelson, in this classical paper, showed by a series of careful experiments, that the growth response noted by Hume could be produced in animals fed on a diet deficient in vitamin A in two ways; by irradiation of the animals, and by the administration of cod liver oil in which the vitamin A had been destroyed by aeration according to the method of McCollum (32). This recognition by Steenbock and Nelson of the existence of an anti-rachitic vitamin as distinct from vitamin A, led to the correct interpretation, i.e., that two vitamins were present, one vitamin A stored to some extent in the animal body, and the other the anti-rachitic vitamin supplied by light. It led furthermore to a revision of the experimental technique with the use of various "vitamin A" deficient diets, for it showed that these diets were deficient in the two vitamins, and that in experiments demanding a deficiency of vitamin A only, the anti-rachitic vitamin must be supplied.

The work of Hume and Smith (34) was then continued on the basis of some work of Kestner's, and they tried to find out whether irradiated air had any effect on rats suffering from a deficiency of vitamin A. Their rats were kept in glass jars and bedded on sawdust. They exposed these jars containing the sawdust to radiations from a mercury vapor quartz lamp, and found that rats kept in these jars showed the same response of increased growth that they showed when radiated directly. They were at first inclined to attribute this result to an effect of "ionized air," but in a later paper (35) were alive to the fact that they had failed to exclude the possible effect of irradiation of the sawdust used for bedding, for on repeating the experiments and irradiating empty jars, the results were negative. In a later paper (36) they found it was necessary for the rats to eat the irradiated sawdust for the effect on growth to be produced. They did not discover the mode of action of the sawdust. This was left to Rosenheim and Webster (37) who extracted from sawdust a yellowish resin, which proved, after irradiation, to be completely protective for rats fed on a standard rickets-producing diet. If the facts of these experiments had been correctly interpreted, it would have been apparent that vitamin D had been produced in vivo by irradiation of the animal, and in vitro

by irradiation of the sawdust; also that it was effective in the animal by way of the skin, and also by way of the alimentary tract.

Steenbock and Nelson following the work already mentioned (38) postulated their theory that light was without effect on vitamin A, that the diets deficient in vitamin A in use at this time were also deficient in the anti-rachitic vitamin, and that when the latter was supplied by light to rats fed on the diet, a growth response resulted, which continued until the animal's reserves of vitamin A were exhausted. In other words, they recognized the existence of *two* growth-limiting factors in the diets deficient in "vitamin A," a lack of vitamin A and a lack of the anti-rachitic factor. In a later paper, Steenbock et al. (39) found that cod liver oil in which vitamin A had been destroyed by aeration would restore the blood phosphate and calcium to normal, and increase the ash in bone in chickens and dogs. Their next step was to verify the work of Goldblatt and Soames, who found that liver taken from irradiated rats possessed growth-promoting properties not possessed by livers from non-irradiated rats. They found that muscle, irradiated after removal from the body acquired growth-promoting properties.

Proceeding on their assumption that failure to grow in animals deprived of "vitamin A" was due in part to the lack of the anti-rachitic factor they *radiated their basal diet before feeding it.* One should emphasize here that the important discovery that followed was the logical outcome of the work that went before. They found that irradiation rendered the diet growth-promoting for animals fed on a diet deficient in vitamin A and the anti-rachitic factor, and also that the ash content in the bones of the rats receiving it was *increased* over that of the rats receiving the non-irradiated ration. The final step in proof of their theory that light supplied the anti-rachitic factor only was taken when Steenbock and Nelson (40) proved indisputably that McCollum's 3143 rickets-producing diet could be made, after irradiation, protective.

Coincidently with Steenbock and Nelson (41) Hess (42) read a short preliminary report, before the American Pediatric Society in Pittsfield, Mass., of experiments in which he claimed to have activated cottonseed oil and linseed oil by exposure to radiations from a mercury vapour quartz lamp, so as to make both these inert oils anti-rachitic.

A full report of this work was published shortly afterwards in a series of papers by Hess and Weinstock (43, 44, 45, 46) in which they showed that cottonseed oil and linseed oil were made specifically active by irradiation, and thereby demonstrated the production of an anti-rachitic factor "in vitro and outside the living organism." At the same time they found that certain green food substances, green wheat shoots, and lettuce leaves could be rendered active by irradiation.

This important discovery, made simultaneously and independently by Steenbock and Nelson, and by Hess and Weinstock, of the possibility of rendering inert substances anti-rachitic by irradiation, made it clear that in the cure of rickets by light, a *photochemical process* was involved. The problem to be solved next was to isolate the chemical substance activated in food, in green vegetables, and in the animal body, under the action of radiation.

In 1923, Steenbock, Jones and Hart (47) found that the ether extract of saponified cod liver oil was as efficacious in preventing rickets as the untreated oil, and proved that the anti-rachitic vitamin was therefore present in the unsaponifiable fraction.

In 1924, Hess and Helman (48) found it possible to activate, by means of irradiation, the unsaponifiable fractions of cottonseed oil and linseed oil.

The experiments which led to the discovery of ergosterol

The work which led to the discovery of ergosterol, which we believe to be, in all probability, the precursor of vitamin D, was carried out, simultaneously and independently, by Rosenheim and Webster in England, and by Hess and his co-workers in America. The work of these authors forms an extremely interesting and most important chapter in the history of the etiology of rickets, and is of added scientific value because by slightly different paths the two groups of investigators reached the same goal.

In 1925, Rosenheim and Webster (49) started to investigate the chemistry of the anti-rachitic vitamin or vitamin D. By this time the work of Steenbock and Black, and of Hess and Weinstock on irradiated foods had appeared, and Rosenheim and Webster sought for substance that might be present in the "fatty secretions of man, animals, and in vegetable oils." The work of Ritter and Schlutz who

found that pure cholesterol could be changed by exposure to light with a resulting drop in melting point of some 30°C., and a change in color, led them to think of cholesterol as a substance sensitive to photochemical change. They were also led to suppose, by some unpublished experiments of their own that a fat-soluble vitamin might be associated with cholesterol. It was also obvious that cholesterol was present in the fatty secretions of man and of animals, and phytosterol in vegetable oils; so that they started to investigate these substances on the assumption that light had a photochemical effect which resulted in the production of "an anti-rachitic vitamin." They found, first of all, (in confirmation of the work of Schlutz) that exposure of "pure" cholesterol (from brain) to the mercury vapor quartz lamp for 5 hours at 5 cm. caused a drop in melting point of 23°C. Sitosterol from wheat, similarly exposed showed a drop of 16°C. Coprosterol, from dog's feces, a drop of 41°C. They then proceeded to irradiate cholesterol, in an atmosphere of nitrogen, and to test its biological activity on rats fed on a standard rickets-producing diet, using the x-ray evidence and results of blood analysis for P as their criteria. They found in their first experiments (49) that a daily dose of 0.2 mgm. was ineffective, but that 4 mgm. was completely protective. They then (50) used an exceptionally pure specimen of cholesterol prepared from ox brain (melting point, 149°C.). This had been purified by some twenty recrystallizations, and after a series of experiments on the best method of activating it, they adopted a period of 1 hour's irradiation in an atmosphere of nitrogen. They found that they could, in this way, obtain a substance which was active in doses of 4 to 5 mgm. They then *fractionated* the cholesterol, with the idea of removing the unchanged fraction and concentrating the active fraction. By crystallization with alcohol and light petroleum, they obtained three successive fractions from 1 gram of the original irradiated material. Results of feeding experiments showed that the first fraction, i.e., the crystals obtained by recrystallizing from alcohol of the cholesterol, irradiated in N for 40 hours, was inactive, but could be reactivated by subsequent exposure to the lamp. The other two fractions from the mother liquor gave only partial protection.

With a view to the removal of sterols, precipitation with alcoholic solution of digitonin was the next step. They took 1 gram of irradi-

ated cholesterol (irradiated in an atmosphere of N) and recrystallized it from 10 cc. of absolute alcohol. They precipitated the residue recovered from the mother liquor (0.2120 gram) with excess of alcoholic digitonin solution, and recovered 99.9 per cent of the cholesterol as digitonide. Results of feeding experiments showed that the fraction not precipitated by digitonin gave a partial protective result with rats in doses of 0.01 mgm. whilst the material before fractionation was completely protective in doses of 5 mgm. The investigators at this stage were under the impression that they had isolated an active fraction from cholesterol which they apparently did not regard as arising from an impurity. The activity of this active fraction, however, represents less than half of the activity of the original substance. They were led to regard it as an impurity in later papers (51, 52) when they found that by converting "pure cholesterol" into the dibromide and reducing the latter with sodium amalgam to cholesterol, they produced a really pure cholesterol, which could not be activated by irradiation.

They had already (50) tried to activate ergosterol, prepared from ergot, as being a typical myco-sterol, highly unsaturated and unstable; this they found to be highly protective "even in doses of 1 mgm.," but apparently did not, at this time, suspect that this substance might prove to be a "pro-vitamin." Their digitonin experiments convinced them that it was impossible to convert more than 0.1 per cent of cholesterol into an active substance.

At this time, they continued their investigations partly in collaboration with Professor Windaus of Göttingen. Windaus had found that ergosterol, a highly unsaturated sterol, could not be recovered unchanged from its bromide. Its original discoverer, Tanret (53, 54) had found it to be sensitive to light and to oxidation by air. These facts led Rosenheim and Webster to think, that, as they had already found it highly active after irradiation, it might prove to be the precursor of vitamin D. Their results showed them to be correct in this assumption.

On the basis of the work of Heilbron, Kamm and Morton, who showed by spectrograms that the characteristic absorption band of "cholesterol" was at 280mμ, they compared the absorption spectrum of cholesterol with that of ergosterol. They found an absorption

band in the spectrum of ergosterol at 280mμ some 1500 to 2000 times as strong as that of "cholesterol." They argued from this that if the pro-vitamin were ergosterol the amount present in association with ordinary cholesterol would be of the order of 0.05 per cent, or 1 part in 2000. This substance would, therefore, be active in correspondingly small doses. Tests with rachitic rats confirmed this, for they obtained protective results with astonishingly small doses. 0.0001 mgm. was found to be the protective dose in their final tests, and these values have been abundantly confirmed by other investigators.

They conclude "These results seem to justify the conclusion that the naturally occurring parent substance of vitamin D, if not ergosterol itself, is a highly unsaturated sterol of similar constitution."

The experimental work of Hess and his co-workers on the chemistry of vitamin D began after the publications of the articles already referred to (42, 43) on the activation of inert oils, green wheat and green lettuce by irradiation. Hess, Weinstock and Helman (48) also found the unsaponifiable fractions of linseed and cottonseed oils to contain the active factor after irradiation. Following this, there appeared a series of eight papers dealing with the activation of phytosterol and cholesterol. In the first of these, Hess, Weinstock and Helman (55) followed the lead of their work on irradiated cottonseed oil and isolated phytosterol from the unsaponifiable fraction of 1 liter of the oil. They state that it could not be rendered absolutely pure. One-fourth cubic centimeter of a 1 per cent solution of this, after irradiation, was found to be protective against rickets in rats while similar doses unirradiated were non-protective. Their criteria for determining the potency of the various substances tested was the same as that of Rosenheim and Webster, i.e., x-ray evidence, and the determination of the blood P in rats fed on a standard rickets-producing diet. They did similar experiments with cholesterol, prepared from brain tissue and purified. The substance they used had a melting point of 147.5°C. They found 0.25 cc. of a 1 per cent of this protective after irradiation, while similar doses unirradiated were non-protective. These authors were attracted by the possibility, which has attracted and baffled many other investigators, of finding a rôle for cholesterol in bodily metabolism. Since the part played by cholesterol, in spite of its

widespread occurrence in the body, is unknown, one can readily understand their enthusiasm over these first results. For it appeared as though it might be possible to show that cholesterol played a definite rôle in becoming activated under the influence of light, and reaching the bones by way of the blood stream. In a later paper, Hess and Weinstock (56) became interested in the fact that cholesterol was an unsaturated sterol with one double bond. They reasoned that if the action of light took place at this bond, the irradiation of saturated sterols would give substances of negative value in the cure of rickets. Experiments with dihydrocholesterol, and dihydrophytosterol were tried, and it was found that the theory held; these substances could not be activated by irradiation. They then found (57) that prolonged irradiation destroyed the activity of cholesterol. This loss in activity was associated with the fact that the substance became opaque to certain wave-lengths in the ultra-violet to which, when active, it was transparent. They found the opaque inactive material had developed a yellowish color, and a drop in melting point, as compared with the active substance. The saturated sterols, dihydrocholesterol, and dihydrophytosterol did not undergo any spectral change on irradiation. The next step was an attempt by Hess, Weinstock and Sherman (58) to concentrate the activated cholesterol, with the idea of making it more potent. They took 10 grams of irradiated material and isolated 4 fractions by a series of successive recrystallizations from 95 per cent alcohol. They expected to find increased potency with increased recrystallizations. To their surprise, they found that the recrystallized fractions became less, rather than more potent, the last fraction being the least effective of all. They also found that it was impossible to reactivate the last fraction by irradiation. They concluded from this that, under irradiation, a substance different from cholesterol was formed, and that the process was not reversible. They next prepared (59) a very pure cholesterol by saponification with alcoholic potash and ether extraction of the sterol. This they recrystallized fifteen times. They found it, when irradiated, biologically active in the usual doses, and convinced of its purity, concluded "the activation of cholesterol does not seem to be due to impurities, but to the action of the rays on the sterol itself." In further support of their "double bond" theory, they found it pos-

sible to activate an "unsaturated ester" of cholesterol, namely, cholesterol acetate. They next (60) were induced by a recent paper of Beumer (who showed that activated cholesterol could be separated into digitonin-precipitable and non-precipitable substances) to continue experiments with cholesterol digitonide. They had previously found (59) that irradiated cholesterol had a greater power to inhibit the hemolytic action of digitonin on red blood cells, than unirradiated cholesterol. They separated an active fraction (60) from cholesterol by removal of the digitonide. The active fraction represented only 4 to 5 per cent of the original irradiated cholesterol. Their discovery that the activation of cholesterol was due to the presence of an impurity followed the same discovery made by Rosenheim and Webster (51). Also in collaboration with Windaus, Hess found (61, 62) that the active fraction could be destroyed or removed by bromination. He also tested *ergosterol*, which, when irradiated, he found to be potent in doses of 0.003 mgm. for the rat.

The work of these two groups of investigators has been described in some detail as showing the paths by which the goal was reached. These experiments suggest an interesting possibility with regard to the synthesis of vitamin D in the skin under the action of radiation. These authors found that it was not possible, by fractional crystallization, or by precipitation with digitonin, to effect a complete separation between cholesterol and the "activable sterol." After activation by ultra-violet radiation it was possible by these methods to separate an active anti-rachitic substance from the sterols. It is therefore possible that ultra-violet radiation not only causes the formation of vitamin D in the skin, but that the "pro-vitamin" will remain in the skin until activated; when it will become readily separable from the associated sterols and in this way made available for absorption via the blood stream or lymphatics.

Steenbock and Black (63) continuing the earlier work (41, 64, 38, 40) on irradiated diets were convinced that they were dealing with the formation of vitamin D under the action of light. They therefore continued experiments on the irradiation of various fats and their constituents, using growth, increased ash content of bone, and "line tests" in rats as their criteria of activity. They found that irradiated olive oil, added to the basal diet, raised the ash content in

humeri of the rats from 48.4 per cent in controls receiving unirradiated, to 56.1 per cent in those receiving irradiated oil. The technique of these investigators, in determining the ash content of bone in their rats, was superior to that of Rosenheim and Webster, and of Hess and Weinstock, who used the more subjective criterion of x-ray evidence. Steenbock and Black then worked with the unsaponifiable fraction of olive oil. They found it, after activation, to be very potent, and the same thing was found using the unsaponifiable fraction of cod liver oil. They also found that excessive irradiation of olive oil and of cod liver oil resulted in inactivation, and concluded that the activated compounds were labile, "in the presence of other constituents of these fats." They found that old oils, with an acid reaction could not be activated, but do not regard this as due to an inhibition of the reaction by compounds formed on standing, nor to the presence of acid, because a mixture of unsaponifiable constituents of fresh oil added to the old oil could be made active by irradiation, and also acidification of fresh fats did not hinder activation. In this paper they also report experiments with irradiated cholesterol, which they found to be active, and this activity was *not* destroyed by prolonged irradiation either in crystal form or in ether solution. In a later paper (65) Steenbock and Nelson investigated the sterols of cod liver oil. On the basis of the work of Windaus (66) they decided to use digitonin as a method of removing cholesterol from the unsaponifiable fraction of cod liver oil, and to test on rats the residual material. They found that cholesterol represented 50.4 per cent of the unsaponifiable fraction. They tested both the unsaponifiable fraction of cod liver oil, and the same after the removal of sterols, on rats. "Both preparations were found equally active. The cholesterol was inactive." They conclude here "that the cod liver oil preparation was not deprived of its anti-rachitic potency, by the removal of its cholesterol through the usual methods of precipitation with digitonin." They repeated this experiment, modifying the technique so that the unsaponifiable fraction to be treated with digitonin was first treated with alcohol to remove as much of the cholesterol as possible before the use of digitonin. Results of rat tests showed that the anti-rachitic factor was not destroyed or removed by removal of the cholesterol. The cholesterol removed was inactive, but could be activated by irradiation.

In this experiment these investigators were remarkably near the truth. They had separated from cod liver oil its cholesterol, and found it inactive, while the "sterol-free" fraction of the unsaponifiable fractions retained most of the potency of the original fraction. The cholesterol proved to be reactivatable by light, which showed that it still contained traces of the activatabable material, the majority of which was present in the "sterol-free" fraction.

Summary of the experimental work on rickets which led to the discovery of ergosterol

The recent experimental work on rickets may be summed up briefly as follows: The first step was the production of vitamin D in vivo, by the irradiation of animals fed on diets deficient in the two fat-soluble vitamins A and D. This was followed by the production of vitamin D in vitro, through the irradiation of inert oils, green wheat, green lettuce, and basal diets deficient in the fat-soluble vitamins A and D. These observations indicated that in the cure of rickets a photochemical process was involved, which could be demonstrated both inside and outside the animal body. It was evident that some substance capable of photochemical change must be sought for, common to animal secretions, and the oils of plants. It was then discovered that cholesterol common to animal, and phytosterol common to plant tissues could be rendered anti-rachitic by irradiation. It was found impossible to concentrate the activity of irradiated cholesterol by means of successive recrystallizations, or to convert more than 0.1 per cent into an active substance. The active fraction was not altogether removed or destroyed, by removal of the sterols from cholesterol with digitonin. It was however either removed or destroyed by treatment with bromine, since the cholesterol recovered from the di-bromide could not be activated by irradiation. This made it apparent that the activated fraction of cholesterol, was not cholesterol itself, but minute traces of an associated impurity. It was known that ergosterol, a myco-sterol with three double bonds, was also destroyed by bromine, and furthermore known to be capable of photochemical change. It proved after irradiation *to be the most active anti-rachitic substance known*, and it is thought that in all probability the curative effect of light on the skin is due to its action on a "pro-vitamin,"

which, if not ergosterol itself, is "a highly unsaturated sterol of similar constitution." The last link in the chain of events, the isolation of ergosterol from human skin, has not yet been forged, though Hess (162) has shown that human skin can be made anti-rachitic by irradiation. These findings on the chemistry of cholesterol reveal one fact that should be emphasized, namely that *minute traces* of a "pro-vitamin" substance are sufficient to produce their biological effect. These may be present as impurities in chemical compounds that by all the criteria of analytical chemistry would be regarded as "chemically pure," and yet present in sufficient amounts not only to produce their full biological effect, but to make it possible for this effect to be attributed to the substance rather than to its impurity. The difficulty of obtaining really pure cholesterol is obvious from this work.

The formation of an anti-rachitic substance from cholesterol by polymerization

The work of Bills (67, 68, 69, 70) is of interest since it presents a different approach to the subject of the chemistry of vitamin D. Bills worked with cholesterol which he prepared from cod liver oil. From a solution of this cholesterol in carbon tetrachloride, he isolated by means of the catalytic action of floridin, a polymer, which he calls "tri-cholesterol." Tri-cholesterol proved, when tested on rats, to be non-protective, and furthermore, Bills found it impossible to activate it by exposure to the mercury vapor quartz lamp. On further treatment with floridin and carbon tetrachloride he obtained from tri-cholesterol a resinous "degradation product" which exhibited anti-rachitic activity. He therefore appears to have produced an active substance from an inactive one by means other than light. What this substance is, is not understood. It appears to be different from vitamin D and active irradiated "cholesterol."

Clinical use of irradiated ergosterol

Irradiated ergosterol used in the treatment of rickets in infants, has given good results, Höttinger (149), Beumer (150), György (151) and Hess, Lewis and Rivkin (152). Hess et al. regard irradiated ergosterol as a specific in the treatment of both rickets and tetany, and Hess states that "this drug has never failed in rickets; that even

in many cases in which cod liver oil had not brought about healing irradiated ergosterol initiated a rapid cure."

Toxic effect of overdosage

One might predict that a drug, so extremely potent in small doses, would prove to be toxic to the organism if given in excess. Recent experimental work from several sources shows this to be the case. Dixon (137) produced urinary calculi in rats by means of daily doses of 17 mgm. Harris and Moore (153, 154) and Harris and Stewart (155) showed that large overdoses of irradiated ergosterol were followed by the extensive deposition of calcium salts in various parts of the body. These authors have shown that the toxic effect depends upon the concentration of the active substance administered, rather than upon the production of toxic by-products. They were unable to produce toxic effects with over-irradiated, or unirradiated ergosterol.

Kreitmair and Moll (156) and Kreitmair and Hintzelmann (157), working with various animals, have demonstrated deposits of calcium in heart muscle, kidneys, arteries and other organs, together with death of the animal following the administration of large doses of irradiated ergosterol.

These results indicate that a careful standardization of dosage of the drug is necessary before it can be regarded as a safe therapeutic agent. The possibility of a cumulative effect of small doses should also be investigated.

V. TUBERCULOSIS

Clinical

Mayer (71) in 1921 published a critical review of the subject of sunlight and light from artificial sources in the treatment of tuberculosis, with an extensive bibliography. Since this review was written, very little has been added to our knowledge of the subject from the clinical standpoint.

The foundation of Rollier's Clinic in Leysin in 1903 gave great impetus to the use of heliotherapy in the treatment of tuberculosis. On reading the second edition of his book, recently published (72), one is profoundly impressed with the clinical results obtained, especially in bone tuberculosis, by a treatment régime in which helio-

therapy is one of the factors employed. The results given in this book are the fruit of 25 years' experience, and they stand in the foremost rank of the brilliant clinical achievements of our time. Rollier says that the scientific aspects of the effects of heliotherapy are bound up in finding answers to three questions.

1. What rays bring about the cure?
2. In what way do they act?
3. What physiological process is involved in cure?

We are bound to confess that none of these questions has been satisfactorily answered, and that the effect of radiation alone, on bone tuberculosis, is still a matter of conjecture. Rollier, from his clinical observations, regards the effect as due, in the main, to ultra-violet radiation. He finds that pigmentation of the skin predisposes to cure, that ultra-violet radiation only will bring about pigmentation, and argues from this that the curative radiations are in the ultra-violet region. These observations of Rollier's could be explained more logically on the opposite theory. As discussed elsewhere, Peacock (113) gives evidence that pigmentation of the skin is a protective mechanism against the action of ultra-violet radiation. Therefore, it would seem more likely that Rollier's best results have been obtained in cases where the skin of the patient is most effectively protected against radiations in the region of the ultra-violet. Until more is known about selective radiation in the cure of tuberculosis of bone from the experimental standpoint, its specific action must continue to be a matter of speculation. While heliotherapy undoubtedly plays a large part in the results reported at Leysin, we must recognize that it is only a part, not the whole, of the régime. It is at present impossible to evaluate the other factors, but we recognize their existence. These factors are exposure to air exceptionally dry and pure in quality, freedom from fog, dust, winds and rain, combined with ideal conditions of feeding, prolonged periods of rest, orthopedic treatment, and wherever possible, pleasant occupational therapy. These, in themselves, must play a large part in the excellent clinical results obtained. Rollier regards the formation of pigment as of great prognostic importance, on the theory that pigment acts as a transformer which changes rays of short wave-length into rays of longer wave-length with deeper

penetration. This view, as discussed elsewhere, has been refuted by Clark (14) and questioned by many authors.

Mayer (71, 75) regards the rôle of pigment and its mode of formation as still obscure, also the specific powers possessed by pigment as unproven. He questions Rollier's theory that pigment transforms short rays to long rays of more penetrating power, and regards the relationship of pigmentation to prognosis as doubtful. He emphasizes the need for more extended research on the penetrating power of different rays and their effect upon tissues. He reports excellent results following the use of *heliotherapy* with children in the treatment of bone, joint, skin, and peritoneal tuberculosis. In laryngeal tuberculosis the results are doubtful, but the best results were obtained by a combination of general with local treatment. In intestinal tuberculosis the results are doubtful, in some cases he obtained "good palliative results, with cessation of abdominal diarrhea," but this was the exception rather than the rule. In tuberculous adenitis he obtained better results with x-ray treatment than with heliotherapy. With the use of *artificial sources of light* he finds the results in surgical cases on the whole disappointing. He regards the mercury vapor quartz light as an occasional aid in pulmonary cases, but does not exaggerate its value. With regard to the use of sunlight in pulmonary tuberculosis, he realizes that with its use there is the danger of hemoptysis, but thinks it may be used with extreme care in well-nourished, stationary, afebrile cases, but that even in these "brilliant results cannot be promised." He states in conclusion: "Most of the favorable clinical reports of light radiation still rest on empirical evidence. Scientific work has not yet offered us any very helpful therapeutic results."

LoGrasso and Balderry (74) report favorable results with the use of heliotherapy in the treatment of pulmonary tuberculosis. They regard the conflicting opinions as to its value in pulmonary cases as being due to haphazard methods in its use. They report results of 49 cases of moderately advanced pulmonary tuberculosis, treated with heliotherapy. They state that the prognosis in these cases, if they had been treated with the rest cure only, would have been unfavorable. The treatment consisted in a gradual exposure of the whole body to sunlight, reaching a maximum of three hours a day for each patient.

In the height of summer the patients were exposed only in the early morning and late afternoon. The final result on these 49 cases, treated from May to October showed 77 per cent improved, 6 per cent worse, 16 per cent unchanged. These writers conclude that heliotherapy, carefully administered is of the greatest value in the treatment of pulmonary cases, one of its most marked effects being an improvement in general physical condition.

Gauvain (165) gives a summary of his ideas with regard to general light treatment of surgical tuberculosis. This paper is a discussion of "why the results of light treatment in surgical tuberculosis are so variable, why in some instances so brilliant, in others so disappointing." He attempts to explain this on what he calls his "theory of varying stimuli and varying response." He regards sunlight as a non-specific aid to other forms of treatment, and thinks that the important thing for the heliotherapist to study is not the source of light used, but the response of each individual patient to it. He emphasizes, in a paradox, the common "unchanging" factor in heliotherapy as compared with other forms of light treatment as being "that of constantly changing conditions." He insists that the patient should not be stimulated beyond his power of response, and finds that his best results are obtained by the use of a combination of different stimuli, sea-bathing, spraying, paddling, cool sea-breezes as well as heliotherapy. This paper in which the use of heliotherapy in the treatment of surgical tuberculosis is described as "more an art than an exact science," sums up the subject comprehensively.

Experimental

Experimentation on the production of bone tuberculosis in animals has not yet reached a stage where it can be used to determine the effects of radiation in the study of the disease. This is undoubtedly the reason why the clinical results obtained with the use of heliotherapy lack scientific background.

Fraser (77) in a clinical study, found that a large proportion of bone and joint tuberculosis in children in Edinburgh was bovine in origin, and could be traced to infected milk. In a later paper (78) he reviews the literature on the experimental work on the source and origin of bone and joint tubercle. He emphasizes, from a series of

careful experiments, the difficulty of producing in animals, tuberculous lesions in bones and joints. He attempted to infect the medulla of bone with human tubercle and found a tendency for the bone lesion to heal, whilst a generalized infection developed elsewhere. He found the same result from infecting the nutrient artery of the tibia in the rabbit.

Doan and Sabin (79) have recently published some extremely interesting experiments. They studied the effects on the blood of rabbits, which had received an intravenous injection of 1 to 2 mgm. bovine tubercle bacilli. They found that acute cases which died during the first month following injection, showed a generalised tuberculosis of lungs, spleen, lymph glands, liver, with *extensive changes in bone marrow*. They also observed certain changes in the blood which were correlated with the condition of the bone marrow. In animals that survived into the third month, they found that the bone marrow became entirely normal, whilst the disease developed elsewhere "so that one sees the remarkable condition of an animal recovering from the anaemia and leucopenia whilst dying of tuberculosis elsewhere."

These experimental results, although having no bearing on the subject of light in relationship to tuberculosis, have been quoted as indicating an impasse in experimental work which makes a further study of radiation in relationship to tuberculosis difficult. We need a technique for producing tuberculosis of bone in animals, before it will be possible to make scientific study of the effect of radiation in its cure. Until the difficulty of localising the infection of tubercle in bone has been overcome, and an experimental technique with animals has been established, the study of radiation in relationship to tuberculosis must rest on its present empirical foundation. The clinical results with the use of light in this disease are however good enough to warrant further experimental study.

VI. SKIN DISEASES

Laurens (22, pp. 9–17) has reviewed the subject of the physiological effects of radiation on the skin from the standpoints of penetration, the production of erythema and pigmentation, the function and origin of pigment, and the histology of the irradiated skin, in great detail.

This work forms a valuable introduction to the subject from the standpoint of the physiologist, and merits careful study.

One of the earliest observers of the effect of solar radiation on the skin was Bowles in 1888–1893 (80, 81), who studied the effects of Alpine sun in producing sunburn. He was impressed by the fact that sunlight, reflected from fresh snow, had a more "energetic action" on the skin, than the incident ray. He recognized the fact that sunburn was associated with factors other than heat.

Clinical

Finsen was the pioneer in the clinical use of artificial radiation. He founded his Light Institute in Copenhagen in 1896 (83) and his studies gave great impetus to the use of radiation from the carbon arc lamp. His method of treatment was to pass the radiations from a carbon arc lamp through rock crystal lenses so as to concentrate the light, with a layer of water placed between the lenses to absorb heat. He constructed also a compression apparatus which he used to render tissues bloodless, so that the absorption of the "chemical" rays took place in the skin only. The aim of this treatment was to attack diseased tissue from outside, without any injury to healthy tissue. His best results were obtained in the treatment of *lupus vulgaris*, where in a large series of cases treated by local irradiation of the skin, he reported 60 per cent cures. Finsen died before the use of general light baths was combined with local treatment, but before his death he was of the opinion that this should be put to the test. His great contribution was perhaps a recognition of the therapeutic value of "actinic" as distinct from heat rays, and the method he devised to eliminate the latter in the treatment of tuberculous lesions of the skin.

An account of the activities of Finsen's clinic, subsequent to his death, is given by Reyn (85) who found that by a combination of local with general irradiation treatment he was able to raise the percentage of cures in cases of lupus vulgaris from 60 to 90 per cent.

The value of Finsen's radiation treatment in the cure of lupus vulgaris has been confirmed by many writers; the treatment, on the whole, however, has not yielded such a high percentage of cures in the hands of other workers.

Sequeira (86) introduced the Finsen treatment into the London

Hospital, England, and found, in his early cases of lupus vulgaris, using both local and general irradiations, that the results were very satisfactory. In later papers (87, 88) he claims, in a large series of cases treated over a period of seven years, 70 per cent permanent cures, 11 per cent temporary cures with mild recurrences and 3 per cent completely intractable.

Macleod (89) reports 40 per cent cures and "decided improvement in most of the others" in cases of lupus vulgaris treated by the Finsen method at Charing Cross Hospital, London.

Bizard (90) reports 26 per cent permanent cures, whilst in 20 per cent of his cases the disease recurred within six months. See also Clark (91), Simpson (92) and Heilberg and With (93).

Gauvain (73) introduced the Finsen-Reyn method of treatment into his clinic at Alton, England, and in this paper gives a detailed account of the organization of the light clinic, with a description of the lamps used, and the careful technique employed.

A summary is given below of the main results obtained from the study of a number of clinical papers dealing with the use of carbon arc and mercury vapor quartz radiation in the skin diseases mentioned.

In *seborrhoea* and *rosacea* radiation therapy has proved a useful adjuvant to other remedial measures.

In *eczema* the results are variable and inconstant. There is often a temporary improvement, a relief of itching, and a drying up of exudate, but the disease is apt to recur even during the period of treatment. The therapy has not been found to shorten the course of the disease.

In *lupus erythematosus* the results as to the value of the treatment are extremely doubtful.

In *alopecia areata* the treatment is probably of little use, except in the incipient stage of the disease.

In *psoriasis* the results are, on the whole, good; some authors advocate radiation therapy as the treatment of choice. Severe exposures given locally to the lesions, sufficient to produce an intense erythema, appear to yield the best results. This treatment should be combined with general irradiation of the body. Radiation therapy does not effect a permanent cure but most authors agree that subsequent recurrences can be easily controlled by a repeated course of treatment.

In *vitiligo* it has been found possible to produce definite pigmentation in the vitiliginous patches by exposure to radiation.

In *furunculosis* radiation treatment appears to be the treatment of choice. It is effective in aborting furuncles, and in relieving the tension and pain of an indurated boil.

In *acne* also the results of radiation treatment are uniformly good. The skin lesions clear up rapidly, and though they tend to recur, subsequent attacks can be easily controlled with renewed treatment.

References illustrating above summary. Wise (94) a critical survey. With (95), vitiligo, Bryant (96) eczema. Butler (97) a critical survey. Fox (98) alopecia areata. Reyn (85) results reported from Finsen's clinic. Weinbren and Graham-Hodgson (100) tuberculosis verrucosa. Castle (101) general. Dore (102) a critical survey.

Radiation in the Treatment of Idiopathic Purpura Hemorrhagica

Sooy and Moise (163) found that exposure to the mercury vapor quartz lamp of patients suffering from idiopathic purpura hemorrhagica was followed by a rise in blood platelets. Tolstoi (164) was unable to confirm this. Purpura hemorrhagica is a symptom—complex with a tendency to remissions, therefore, it is difficult to evaluate any form of treatment in this disease. Radiation therapy, although undoubtedly beneficial in certain cases, cannot be regarded as a specific form of treatment. The results obtained by radiation have also been obtained by other methods of treatment such as splenectomy and transfusion.

The skin conditions described in the preceding section have been treated with full radiations from the source of light used (with the exception of the Finsen lamp in which the heat rays are excluded). This includes a range of radiations, from the ultra-violet, through the visible, to the infra-red regions of the spectrum. Very little clinical work has been done with filtered light.

Finsen (82, 84) was of the opinion that the pustules of small-pox were light sensitive, and recommended the use of red shades over the windows in the treatment of the disease. It is of historical interest to note that this method of treating small-pox did not originate with Finsen, but was practised early in the fourteenth century by John Gaddesden, physician to King Edward II of England, Garrison (103), Macleod (89) and probably before this by Gilbertus Anglicus and

Bernard de Gordon (1285–1307). This method of treatment did not postulate any positive therapeutic effect of red light, but was merely a method of excluding "actinic" radiations.

Ahlswede (104) attributes a positive therapeutic effect to "red rays" emitted by a Neon lamp.

Pathological conditions of the skin caused by over-exposure to light

It should be remembered that while certain pathological conditions of the skin are apparently benefited by exposure to radiation, quite a number are quoted in the literature as being caused by excessive exposure to solar radiation. These, although somewhat outside the scope of this article, should be mentioned.

A list of rare diseases caused by over-exposure to light is given by Rasch (3). See also Castle (105).

Experimental

Clark (14, p. 282) has discussed the early experimental work of Hasselbach, Henri and Glitscher on the extent to which light of different wave-lengths penetrates the skin. She concludes as a rough estimate that light of shorter wave-length than 300 mμ is absorbed by the epidermis in a layer of 0.1 mm. thick, and that "the shorter the wave-lengths, the smaller the layer that will completely absorb them." According to Lewis (106), blood serum absorbs wave-lengths shorter than 300 mμ. Normal blood absorbs all wave-lengths shorter than 450 mμ and has two absorption bands at 540 mμ and 575 mμ. In discussing the theory of light action, Clark makes some interesting suggestions; she says, "It is safe to believe that the physiological effects of light have their origin in the photochemical reactions produced when light is absorbed." She also says, "It is safe to suppose that all photochemical reactions are initiated by a change in configuration and velocity of the electrons of the substance absorbing light." "If the incident light has small enough wave-lengths to produce vibrations in the electrons instead of in the molecules and atoms, the absorption of light may result in the escape of electrons from the atoms, with a consequent change in valency, resulting in chemical action." Since this article was written one such photochemical reaction has been demonstrated, which has been discussed fully in the section on rickets. It has been shown that under the action of light, vitamin D is formed from a

precursor in the skin, thought to be ergosterol, or a sterol of similar constitution. Ergosterol, when activated by light, shows very definite changes in its spectrophotometric curve, which indicates a chemical action, as suggested by Clark. At the present time, only one such photochemical effect has been proved, but in further study of the effects of light on the skin, it would seem possible that other photochemical effects may be demonstrated, brought about possibly by light of differing wave-length.

Sonne (107) studied in some detail the mode of action of radiation on human skin. He felt it illogical to attribute the whole therapeutic effect of a general light bath to radiations in the ultra-violet region, and made a special study of the biological action of visible and heat radiations. Laurens (22, p. 11) has reviewed his work in detail; the results seem to point to a heating effect of subcutaneous tissue and blood under the action of visible radiations. Sonne regards this production of heat in the skin as being of positive therapeutic value, and recommends the use of the carbon arc rather than the mercury vapour quartz lamp; the former being a better source of visible and heat radiations. Similar results, on the heating effect of visible radiations on the skin, are reported by Butler (97). The action of ultra-violet radiation on the skin is discussed by Lane (167). Ultra-violet radiation is known to cause a temporary vasodilatation of the capillary walls. With intense radiation the effect can be carried to a point where there is increased permeability of the cell walls.

On certain skins, intense exposure to ultra-violet radiations has produced toxic effects which Harris and Hoyt (108) think may be due to the absorption of rays by tyrosin and phenylalanine in living protoplasm.

Lewis and Zotterman (109) investigated the effects on the skin of exposures to radiations from a Hanovia Quartz burner run at 240 volts and 7 ampères. They exposed isolated areas of skin on the human forearm, for varying periods of time, at a distance of 18 inches from the lamp, and studied the changes in the skin subsequent upon exposure. They found a triple reaction of the cutaneous vessels, a local vasodilation, a reflex dilatation of the arterioles, and increased permeability of the vessel walls. They showed that substances produced during the process diffuse into the surrounding skin, and are

carried away by the lymphatics, so that the reaction of the skin is not confined to the area radiated. They traced the reaction into the surrounding unexposed skin and showed its extension along the lymphatic channels. They emphasize a loss of contractile tone in the blood vessels subsequent to irradiation. The effect they describe is not peculiar to light, but can be produced by other forms of injury, such as freezing.

Pigmentation

The effect of ultra-violet radiation in producing pigmentation of the skin has been discussed by many authors. Clark (14), Laurens (22), Jungling (110) Hausser and Vahle (111). The rays that bring this about must lie between the limits of 290 to 330 mμ, since a skin exposed to sunlight will readily show pigmentation, whilst a screen of ordinary window glass cuts off the effective rays. The function of pigment is not understood. From the clinical standpoint the theories as to its therapeutic value have been expressed in two ways.

1. That the formation of pigment has a positive value, and is a sine quâ non of cure. Bernhard (112) and Rollier (72) to a large extent base their prognosis on the production or non-production of pigmentation in the patient's skin. Rollier's well-known theory of the function of pigment, i.e., that pigment acts as a transformer, which changes rays of short wave-length, to those of long wave-length by fluorescent action, has been questioned by many authors. In opposition to this theory, Clark (14) found pigmented skin, examined under Wood's monochromatic light (which induces marked fluorescence when applied to substances capable of such a reaction) to be entirely non-fluorescent.

2. That the formation of pigment in the skin is of negative, or doubtful value. This view has been expressed by Finsen (82, 83, 84), Reyn (85), Peacock (113) and Mayer (71), and these writers aim at keeping the skin of their patients sensitive to light by avoiding a heavy pigmentation.

Peacock (113) in a study of certain substances that proved to be either fluorescent or non-fluorescent when examined in a beam of ultra-violet radiation, found that vaseline, a fluorescent substance, when smeared over the skin protected it against the action of ultra-violet radiation. He also found the keratinized layer of the epidermis to

be strongly fluorescent. He regards this fluorescence of the skin as a mechanism whereby the skin obtains immediate protection against the action of ultra-radiation, since in fluorescence a proportion of the incident rays are dissipated at the surface of the skin as light. He regards pigmentation as a later stage in the same protective process, and suggests that the appearance of pigmentation marks the failure of fluorescence to protect the skin from excessive radiation. This theory of Peacock's would appear to be supported by the fact that fluorescence and pigmentation seem to vary inversely as each other. He says "If pigmentation of the patient is arrived at as a standard of successful treatment, this is tantamount to producing deliberately in the patient a natural and efficient protection against the very source of treatment employed."

Gauvain (165) takes a less definite view of the therapeutic value of pigmentation. He regards it as being not necessarily synchronous with cure. In general his aim is to give a stimulus calculated to elicit the optimal response of the patient, with or without the production of pigmentation. When such eminent authorities as these mentioned above take opposed views as to the clinical value of pigmentation, only one conclusion is possible, namely, that the matter is not understood and cannot be regarded as settled.

A fact that is not sufficiently emphasized but which is apparent to all clinicians who use radiation therapy, is the enormous variation in the response of the skins of individual patients to light. It is impossible to make any arbitrary classification of these patients into those that pigment and those that do not.

Warren[3] after a two years' experience of the use of high intensity carbon arc lamps (90 ampères and 110 volts) in the routine treatment of patients in a general clinic, has kindly given me the following statement.

> There is no way of knowing, before the commencement of treatment, whether the skin of a particular patient will pigment or not. The classification of patients into blondes and brunettes offers only an exceedingly rough indication of their subsequent reaction. Frequently pale-skinned brunettes, both children and adults, fail to pigment altogether, yet tolerate

[3] Private communication, from the Strong Memorial Hospital, Rochester, New York.

large amounts of "high intensity" radiation without any erythematous reaction. Fair-skinned blondes may "tan" instead of becoming "burned" and tolerate large doses of radiation readily, although this is not the reaction one would expect to obtain. With carefully graduated, identical dosage, patients of the same outward colouring and appearance may react differently; some pigment steadily, others "peel" repeatedly with little pigmentation, others "burn" without any appearance of "tan," and there is an occasional patient whose skin shows no demonstrable reaction to very large doses of radiation. The production of pigmentation or its failure to develop, appears to bear no very definite relationship to prognosis; clinical improvement may occur without pigmentation, and excellent pigmentation may occur with no evidence of clinical improvement, in identical clinical entities without respect to the disease studied.

Until more is known about the factors which control the individual reaction of the patient's skin to radiation therapy, and until these variations in response are satisfactorily explained, the production or not of pigmentation must be regarded as of doubtful prognostic importance.

VII. WOUNDS

Claims for the value of radiation therapy in the treatment of wounds are based almost entirely on clinical evidence. Very little experimental work has been done, and the results so far are inconclusive.

Bernhard (112), who antedated Rollier in the clinical use of heliotherapy, was induced to try the effect of mountain sunlight on the healing of wounds. He claims to have had striking success by this method of treatment, and thinks that the most effective radiations are in the visible and infra-red regions of the spectrum. He does not regard the healing effect of sunlight as being due to the bactericidal effect of light on microörganisms, but to some effect which results in direct stimulation to the growth of epithelium. The work of Torraca (114, 115, 116, 117) would appear to support this, since he found that sterile bandaged wounds artificially inflicted on guinea pigs responded to sunlight more readily than open wounds. On the other hand Coburn and Cowles (118) working with rats were unable to confirm this.

Breiger (119) in an article on light therapy in the world war, summarizes the literature on the treatment of wounds by "ultra-violet light" therapy. In his own clinical work he used the mercury vapor

quartz lamp. He gives an account of an experiment on himself in which a severe over-dose of radiation from 3 new mercury vapor quartz lamps, produced in addition to an extremely severe dermatitis "an unusually dark pigmentation." He found in later trials, using a more moderate dosage that, although he was always able to produce a reaction of erythema in his skin, he was never again able to produce pigmentation. This experiment of Breiger's is of interest as indicating possibly a permanent effect in the skin resulting from over-dosage with ultra-violet radiation. Failure of skin to pigment under the influence of radiation therapy is a common experience in clinical practice; but for a skin, once sensitive to pigmentation, to lose this power, is rare. Breiger thinks that the effect of radiation in the healing of wounds is first to dry them, and then to produce an effect of suction similar to that produced by cupping. He noticed in certain cases a seeding of epithelium over the surface of the wound, under the action of radiation, rather than the usual process of healing from the edges. He thinks that this may be regarded as an "auto-transplantation" of minute particles of epithelium torn off from the surrounding healthy skin which fasten themselves on the surface of the wound during radiation treatment, and so form islands of epithelium. He reasons from this that radiation therapy may be of value in stimulating initial growth of skin transplantations.

Crile (120) has recommended the use of continuous exposure to electric light, combined with Dakin's solution in the open treatment of wounds, and his results with this line of treatment are undoubtedly good. Without doubting for one moment the clinical results obtained by these authors, one is somewhat sceptical as to the validity of the claims for a specific effect of radiation on wounds. It would appear to the critical reader that the main results obtained are produced in two ways, by heat and by a destructive action on bacteria, and that both these results can be, and have been produced by other means. Any source of light rich in ultra-violet and infra-red radiations could bring about both these results. It is very suggestive that Crile (120), using a source of light almost deficient in ultraviolet (bactericidal) radiations, should find it necessary to reinforce it with an antiseptic (Dakin's solution).

Ries (121) found a tendency for vaccination scars to become irri-

tated and red when exposed to ultra-violet radiation, and thinks that all scar-formations should be protected from light, on the theory of its hypersensitiveness to light, especially to radiations in the ultra-violet. This view formed the basis of Finsen's treatment of small-pox already discussed.

The claims for a specific curative effect of radiation on wounds cannot be regarded as proven, neither can the good clinical results attending its use be disregarded; but in general one may say that, at present, radiation in the treatment of wounds is an empirical remedy. No effort has been made to define the region of the spectrum most beneficial, and little or nothing is known with regard to dosage. No attempt has been made to screen out rays that may be harmful, and no one knows definitely whether the good results claimed are due to local or general treatment. Until more accurate observations are made of the effect of radiations on wounds under controlled conditions, we must conclude that the claims made for the value of the treatment lack scientific background.

VIII. DEFICIENCY OF VITAMIN A

Clinical

Clinical manifestations of vitamin A deficiency in infants, such as are seen in the experimental rat are rarely met with, except under conditions of extreme food deprivation; such conditions occurred in Europe during the late war.

The work of C. E. Bloch of Denmark is the most important clinical contribution to the subject we have, and his papers (122, 123, 124, 125, 126), which have been translated into English, are of extreme interest. In his first translated paper (122) he relates, how, in the Children's Department of the State Hospital in Copenhagen, he noticed the occurrence of a certain eye condition in malnourished children. This condition proved refractory to treatment in the Ophthalmic Department of the Hospital, but yielded to the addition of certain fats, notably full milk and cod liver oil, to the diet of these children. His work was published in Danish in 1917 and 1918 and he says "When I published my first paper it was unknown in this country, that the American physiologists had obtained evidence of the presence of certain specific bodies in various fats," and in later papers he recog-

nized the fact that he was fortunate to work at a time when an explanation of his clinical findings was available through the means of animal experimentation. He recognized the eye disease as being xerophthalmia, and correlated the outbreak which occurred in Denmark during the late war with a shortage of fat. At this time all the whole milk and butter was being exported, and only skim milk and butter milk were available for the very poor. From the first (123) he questioned, on clinical grounds, the then-prevalent idea, that rickets is due to the lack of vitamin A. He found that the specific lesion, due to lack of vitamin A, namely xerophthalmia, was rarely met with in association with rickets. At about this time McCollum (32) made his important discovery that rickets in the rat could be cured with cod liver oil in which vitamin A had been destroyed by aeration, and that the same oil was ineffective in the cure of experimental xerophthalmia in rats. In a later paper (124) Bloch showed that in certain cases of xerophthalmia which fail to respond to vitamin A in the diet, there may be an intercurrent infection which interferes with its absorption. At this time the cure of rickets with ultra-violet radiation was well known, and Bloch (124) proceeded to investigate the effects of radiation treatment on xerophthalmia. He used full radiations from a 75-ampère carbon arc lamp, in the treatment of two mild cases, a brother and a sister. During the period of treatment these two children were fed on a diet containing, as Bloch showed later, enough vitamin A to control the disease, but not enough to bring about a cure. Full details of the diet are given in the paper. The boy received 17 light baths and the girl 11, of two hours' duration every other day, with the lamp "brought as near . . . . as possible," and the skin in both cases became rapidly pigmented. The result in both cases was no cure, but no intensification of the disease; a result which Bloch showed could be brought about by the diet alone. He concludes that light cannot replace vitamin A, or supply it to the organism.

Experimental

Luce (127, 128) showed that exposure of the animal to sunshine played no part in increasing the vitamin A value of cow's milk as tested on rats suffering from a deficiency of "vitamin A." By keeping

one cow under varying conditions of light and diet for a period of two years, the vitamin A value of the milk was shown to vary within wide limits, but these limits of high and low values proved to be directly proportional to the vitamin A content of the diet of the animal. The exposure of the cow to sunlight had no significant effect in raising the vitamin A value of the milk. This work was carried out before the distinction between vitamin A and vitamin D was fully recognized, and the basal diet of the rats, used by Luce in the titration of the milk, is open to the criticism that it was deficient in both vitamins. This work was continued by Chick and Roscoe (129), using the same experimental cow. These workers modified the basal diet of the rats, and supplied vitamin D by the addition of irradiated cotton seed oil. They also found exposure of the cow to sunlight to be without effect in raising the vitamin A value of the milk.

Powers, Park and Simmonds (130) found that rats fed on a diet deficient in vitamin A, and exposed to sunlight, were not protected against xerophthalmia. They found, however, that the exposure of the animals to sunlight did delay to some extent the development of xerophthalmia, and prolong the period of survival of the animals on the diet. Their experiments indicate that sunlight cannot be used as a substitute for vitamin A. Similar negative findings as to the value of radiations from an artificial source to supply a vitamin A deficiency in the diet of young rats are reported by Sheets and Funk (166).

The writer, in a series of unpublished experiments, has tested a series of isolated radiations, in the ultra-violet, in the visible, and in the infra-red regions of the spectrum, on rats fed on a standard diet deficient only in vitamin A. These radiations were transmitted through filters from the same source of light; a carbon arc lamp (25 ampères and 110 volts). Seven groups of rats received a daily irradiation; each group was irradiated with a band of radiations transmitted through one of the seven filters, and the animals were kept for the remainder of the time in a photographic dark room. She was unable to obtain any evidence of a protective effect of any of the radiations used. The rats that received ultra-violet radiations were, if anything, made worse by the treatment.

Coward (131) found that light from a mercury vapour quartz lamp was effective in causing an acceleration of the formation of vitamin A

in living plant tissue, without influencing the ultimate amounts of the vitamin contained in the tissues. She also found the amount of vitamin A in etiolated wheat shoots to be an inverse function of the temperature at which they are grown.

The weight of both clinical and experimental evidence seems to show light to be without effect on disorders arising in the child, and in the animal, from a deficiency of vitamin A. It cannot therefore act as a substitute for vitamin A, which must be supplied in the food. Light has a definite effect on plant tissue in hastening the production of vitamin A, and so has heat; but whereas heat in general doubles the rate of vitamin A production for every 10° rise of temperature, light will produce the same effect more rapidly.

IX. DISEASES OF THE EYE

There is a large and important literature dealing with the effects of light on the eye; the absorption characteristics of the various eye media, and the pathological effects of certain radiations in the production of snow-blindness, glass-blower's cataract, senile cataract, and conjunctivitis. This is, however, outside the scope of this review.

With regard to the use of radiation in the treatment of diseases of the eye, Lundsgaard (132) working at the Finsen Institute in Copenhagen regards the Finsen Light treatment in tuberculous disease of the eye as being of doubtful value. In cases of extreme photophobia, he found that exposure of the patient to a general light bath (with the eyes covered) proved beneficial, but not as beneficial as the use of sun baths under the same conditions.

Nutt (133) recommends the use of full radiations from a quartz Hanau lamp, to the entire body, with eyes protected with smoked glasses, in the treatment of phlyctenular conjunctivitis. This treatment is combined with daily doses of cod liver oil. He finds that the treatment results in the disappearance of blepharospasm and lacrymation, and that the phlyctenules clear up gradually.

See also Castresana (134).

X. GENERAL NUTRITION AND RESISTANCE TO INFECTION

Clinical

Many claims have been made for the beneficial effects of artificial light therapy in promoting growth and resistance to infection in chil-

dren. These claims would appear to be rooted in subjective rather than objective evidence, and in support of this statement two well-controlled clinical studies may be quoted: that of Mackay (11) and that of Barenberg and Lewis (146).

Mackay (11) made observations extending over a period of 13 months, on the effects of treatment with the mercury vapour quartz lamp on the health of infants. These infants were taken from the out-patient department of a London Hospital, were artificially fed, and sub-normal in weight and general health at the beginning of the investigation. 66 were treated with light and 137 were used as controls. All the children were given cod liver oil with a view to eliminating rickets as a complicating factor in the investigation. During the course of the investigation both groups of infants were studied from the standpoint of weight, percentage of hemoglobin in the blood, resistance to infection and general clinical condition. It was found that the rate of gain in weight in the light treated cases was approximately equal to that of the controls. Light treatment did not cure or prevent the development of anaemia, neither did it protect against the occurrence of respiratory infections. No objective evidence was obtained for the value of radiation therapy in improving the general clinical condition of the children.

This study of Mackay's is of special value inasmuch as her results were subjected to careful statistical analysis. She was also careful to note and evaluate every possible source of error in such an obviously difficult investigation. She states, "different results might have been obtained with another type of lamp, e.g., the carbon arc," but a similar study with the use of the carbon arc lamp made by Barenberg and Lewis (146) gave, on the whole, similar results.

These authors studied the effect of carbon arc radiation on the health of a group of 9 infants treated in an institution, over a period of three months, using a similar group of 10 unirradiated infants as controls. The dietary regime of both groups of infants was the same and included a daily dose of cod liver oil. They found that radiation treatment had no effect in reducing the incidence of respiratory infections. Growth in weight and in height during the first six weeks of treatment was greater in the irradiated than in the non-irradiated group, but during the second six weeks the converse was observed.

Blood counts showed that the number of erythrocytes and leucocytes did not seem to be affected by irradiation. Radiation appeared to prevent a 12 per cent fall in hemoglobin which was noted in the unirradiated group.

These authors think that radiation produced an initial stimulating effect, which was followed by a depressant action of the rays. Their results suggest that an initial benefit may be lost by over-irradiation, but do not on the whole give any very weighty evidence for the value of the radiations used.

Experimental

Hill and Clark (147) investigated the effect of ultra-violet radiation on the resistance of albino rats to a pneumococcus infection. Their results as to the value of the radiations used were completely negative. They say in conclusion, "The present state of our knowledge concerning the effect of ultra-violet radiation on susceptibility to infection does not justify its use as a general therapeutic agent in infectious diseases and gives very little support to the belief that it is capable of increasing natural resistance in normal individuals."

Wade Brown (158, 159, 160) made a careful and exhaustive study of the effect on normal rabbits of continuous exposure to radiations from a Neon light. This lamp emits a band of radiation between the limits of 337 and 362mμ, but by far the greater part of its radiation lies in the visual red and near infra-red regions of the spectrum between the limits of 580 and 760mμ. He found that albino rabbits kept in this light environment showed a gain in weight that was approximately three times that of a control group. This gain in weight was accompanied by increased proliferative activity of hair follicles over shaved areas of skin and increased functional activity of certain organs.

The author (161) has shown a growth-promoting effect on rachitic rats, of daily short exposures to isolated radiations in the near infra-red region of the spectrum between the limits of 720 to 1120mμ.

It is possible that the results of both these experiments will be traced to a hitherto unsuspected photochemical effect of infra-red radiation on the organism, although at present this is nothing but a tentative suggestion. Wade Brown thinks it more likely that the profound influence of a fixed light environment on the animal organ-

ism demonstrated in his experiments does not depend on the wavelength or energy equivalent of the light concerned.[4]

XI. SCREENS FOR THE TRANSMISSION OF ULTRA-VIOLET RADIATION

A great deal of interest has recently been shown in the development of screens capable of transmitting the ultra-violet radiations of sunlight. Many such screens are now on the market and are being widely advocated under different trade names, for use in hospital solaria, animal houses, schools and offices. These various glass materials vary considerably, not only in their initial transmission, but in the degree to which they deteriorate after prolonged exposure to light.

A summary of the transmission data of all these glasses and glass substitutes (such as cellulose acetate) used for therapeutic purposes has been published by Coblentz (147a). In this paper Coblentz emphasizes the fact that all the new glasses on the market that transmit the ultra-violet radiations of sun-light, decrease in the power to transmit these rays on exposure to light. This fact should be borne in mind when considering the advisability of going to the expense of installing these glasses on a large scale.

Clark (148) estimated the probable amount of ultra-violet radiation obtained indoors through one of the best of these ultra-violet transmitting glasses. She took into consideration the fact that a worker indoors would not sit in the direct sunlight, and assumed an average illumination of 10 foot-candles. She found that the amount of ultra-violet radiation through this screen reaching a point inside a room, where the illumination was 10 foot-candles, was so small as to be incapable of direct measurement. By indirect measurement (the zinc sulphide method (Clark (12), she estimated that "a child would have to sit in that place for 20 hours to get as much ultra-violet radiation as he would get in two minutes out-doors in sunlight at noon." This paper indicates that the expense of installing these ultra-violet transmitting glasses in schools and offices is hardly justified in view of the doubtful benefit derived. Their use in hospital solaria specially

[4] Since going to press the following report by Dr. Dora Colebrook (Medical Research Council—Special Report Series No. 131) has appeared. Dr. Colebrook studied the effect of artificial irradiation on the health of school children. Her findings as to the value of the radiations used were of a negative character.

constructed to obtain the maximum amount of direct sunlight during the day, is another matter. But even here, as Coblentz (147a) points out, "it requires but little dust and dirt to reduce the transmission by 40 to 50 per cent."

XII. POSSIBLE DANGERS OF RADIATION THERAPY

1. Accident may be caused by the use of lamps of faulty construction. A case (135) was recently reported in England of a young man found dead in a bath, with an "ultra-violet" lamp beside him. He had suffered from acne, and had evidently bought the lamp for the purpose of self-treatment. The lamp was of faulty construction, improperly insulated, and the man died from electrocution.

2. Accidental overdosage. MacCormack and McCrea (136) report the case of an old man who fell asleep during a self-administered treatment from a therapeutic lamp, the details of which are not given. He received an exposure lasting one hour and ten minutes instead of the customary ten minutes. This accidental overdose was followed by a grave constitutional illness.

3. Possible effects of overdosage causing an over-production of vitamin D in poorly nourished persons. In a recent article, Dixon (137) showed that urinary calculi can be produced in rats by the administration of large doses of irradiated ergosterol. Padua (138) concludes from a study of the incidence of urinary calculi among Filipinos that "inadequate dietetic conditions amongst Filipinos and concomitant nutritional disorders such as beri-beri favor the formation of phosphatic stone." Dixon suggests that the formation of urinary calculi reported by Padua might be further explained on the basis of excessive exposure of the Filipinos to sunlight. This, combined with their poor dietary regime, might lead to an over-production of vitamin D followed by the formation of urinary calculi. If substantiated, this suggestion of Dixon's would indicate the possibility of a specific danger involved in the use of excessive exposures to radiation of poorly nourished persons.

4. Harmful effects of radiation therapy in certain diseases. These have been discussed more fully elsewhere, but should be mentioned here. Radiation therapy appears to be definitely contraindicated in certain cases of active pulmonary tuberculosis, where its use has been

found to cause hemoptysis. In cases of heart disease and nephritis radiation therapy has also proved more harmful than beneficial. See also Heald (139).

In a recent article Dixon (140) makes the rather general statement that the opinion of physicians in general deprecates the use of radiation in the treatment of "highly nervous and neurotic people" on the ground that it may cause a "grave psychic reaction." Mudie (141) has criticized this statement on the basis of his own clinical experience. Drury (143) investigated the effects of ultra-violet radiation in the treatment of mental disease. He found that "agitated melancholies, acute maniacs, and epileptics" do not benefit mentally, but become worse. "Simple melancholias and manic-depressives" showed an improvement in physical condition after radiation, which led to some improvement in their mental state.

XIII. THE PROTECTION OF THE PUBLIC AGAINST THE INDISCRIMINATE USE OF "ULTRA-VIOLET" LAMPS

In view of certain dangers attending the use of radiation, the question arises as to whether radiation therapy should not be exclusively in the hands of people specially trained to administer it.

There is a general feeling in the minds of the public, that x-rays and radium are dangerous except in the hands of an expert, but with regard to ultra-violet radiations no such feeling exists. The carbon arc and the mercury vapor quartz lamp are on the market for any one to buy and install in his home for indiscriminate use. Steps have already been taken in England, France and the United States to protect the public against the dangers involved.

In England a special sub-committee of the British Medical Association was appointed to consider how best to safeguard the use and do away with the abuse of radiation therapy in general. The final form of its recommendation was quoted by Heald (142) at a discussion in the Section of Radiology and Physiology at a recent annual meeting of the British Medical Association. This recommendation is as follows:

> That in view of the risks to the public involved in the use of electricity and radiation as methods of treatment by untrained and unqualified persons it is to be desired

(1) That suitable courses of training should be organized under medical direction for persons who wish to administer this form of treatment.

(2) That persons who have satisfactorily followed such a course should be entitled to have their names entered on an approved Roll.

(3) That one of the conditions attached to admission to, and maintenance on, the approved Roll should be abstention from the treatment of any patient except on the responsibility, and under the general supervision of a registered medical practitioner, and

(4) That patients who require electrical or radiation treatment should be referred only to these persons whose names are in the approved Roll.

Heald (142) also quotes the Council of Public Hygiene in France.

That given the serious accidents which may result from the use of ultra-violet radiations handled by incompetent persons, it is necessary in the interests of Public Health to confine the use of these procedures to hospital services, and to authorise their application only by specialist physicians.

In the United States the Council of Physical Therapy has reported on the dangers to the public of self-treatment by the sale of generators of ultra-violet energy. The Council (144) is convinced "that the sale of generators of ultra-violet energy to the public for self-treatment is without justification" on the following grounds: (1) The danger of ultra-violet burns and injury to the eyes; (2) the inability of the lay public to judge what cases are suitable for radiation treatment; (3) that the possession of lamps would encourage the public to make their own diagnoses and deprive them of expert advice; (4) that such practice would encourage the sale of fraudulent and useless lamps.

These instances show that at the present time expert opinion is alive to the dangers involved in the indiscriminate use of radiation by the laity. This attitude has ample basis, for in certain conditions radiation therapy is positively harmful. The treatment is comparatively new and we have yet to find out its latent effects. We know very little about dosage, and have no means of measuring it except the empirical criterion of a dose that will produce a skin erythema. In one disease only, namely rickets, have we a sound scientific basis for the use of radiation; the curative radiations in this disease are limited to a very narrow band in the ultra-violet, and with regard to the effect of rays of longer wave-length we know very little. In

general one may say that at the present time our lack of knowledge as to the effects of radiation on the human organism is an outstanding fact. This alone would appear to be sufficient argument to justify any legislative action to protect the public against its wholesale use as a general panacea.

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